Idiotype Vaccination in Follicular Lymphoma: Knocking on the Doorway to Cure

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Follicular lymphoma is a tempting therapeutic target. Happily for both patients and physicians, the disease often responds to therapy. A wide range of treatments produce tumor regressions, including single-agent and multiagent chemotherapy; localized and targeted radiation therapy; cytokines such as interferon-α; monoclonal antibodies directed at various cell surface molecules, such as immunoglobulin and CD20; and targeted therapies that interfere with cell functions, such as antisense RNA to bcl-2 and the proteasome inhibitor bortezomib. The various combinations of these modalities are also effective at causing tumor regressions. Indeed, some combinations of these agents (for example, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab [R-CHOP]) can produce objective responses in nearly 100% of patients (1).

The history of oncology has taught us that when a tumor is responsive to treatment, particularly to many kinds of treatment, by combining active weapons we usually find a way to cure at least a subset of patients—and, in some cases, a great majority of them. Follicular lymphoma has been an exception to the rule. Radiation therapy can induce long-lasting remissions in the small fraction of patients with localized disease. Yet the majority of patients have advanced-stage disease, and, despite the many agents that induce tumor regression, it has been difficult to ascertain whether any treatment can prolong survival in patients with advanced-stage follicular lymphoma.

Why is that? Follicular lymphoma poses a variety of unusual obstacles to assessing the value of treatment. First, patients can live quite a long time with disease. Unlike many other cancers in which disease recurrence after treatment is a harbinger of death (that is, disease-free survival and overall survival are nearly parallel lines separated by only a few weeks or months), patients can live with measurable follicular lymphoma for many years, even decades. In the past, patients were routinely treated in an attempt to induce complete remission. They often achieved complete remission. Within about 2 years, they relapsed. We treated them again. They responded again. They relapsed again. We treated them again, and so on. Median survival was 10 or 12 years in some series. This long natural history could seduce one into thinking that therapy capable of inducing responses was responsible for the survival. However, Carol Portlock and Saul Rosenberg disabused us of that illusion in 1979, when they reported prolonged survival of a subset of patients with follicular lymphoma who were managed with a “watch-and-wait” philosophy employing no initial therapy and treating only palliatively when any treatment was needed (2). This small series of patients demonstrated that prolonged survival was possible even if no attempt were made to eradicate the disease.

A second barrier to determining therapeutic benefit in follicular lymphoma is the fact that some patients with measurable disease do not experience progressive tumor growth and others actually have objective tumor regressions in the absence of any antitumor therapy (3). Such spontaneous remissions were not anecdotal, as they are in renal cell cancer. Fifteen percent or greater of patients with follicular lymphoma may experience spontaneous disease regression without treatment. We just cannot tell prospectively which patients they are.

A third hurdle in assessing the value of therapy in follicular lymphoma is the endpoint problem. The ideal endpoint to measure therapeutic effect is overall survival. The therapy either prolongs survival or it does not. If the average patient lives more than 10 years, the average investigator would not be able to do more than two or three studies in an entire career if overall survival is the endpoint one attempts to alter with therapy. Trust me on this one. My colleagues and I began a randomized trial of aggressive therapy versus watch-and-wait in indolent lymphoma in 1978. Nineteen years later, with a median follow-up of 13 years (unpublished data), huge and statistically significant differences were seen in the number of patients in complete remission on the two arms. But overall survival was identical. In the aggressive treatment arm, the
majority of patients were in their initial complete remission and alive, free of disease. By contrast, 75% of patients managed initially with watch-and-wait were alive with disease—but they were alive. We are good at keeping patients with follicular lymphoma alive. Thus, overall survival is not an achievable endpoint for a therapeutic trial in follicular lymphoma.

What endpoint should we use? Many are advocating disease-free survival as a surrogate endpoint. However, using disease-free survival as an endpoint is problematic. Before Portlock and Rosenberg revolutionized our thinking about the disease, we routinely kept patients disease free with intermittent cycles of combination chemotherapy such as cyclophosphamide, vincristine, and prednisone (CVP). I have had patients who remained clinically free of disease for many years with a cycle of CVP every 3–4 months. I do not know if I have prolonged their survival (or, indeed, shortened it), but they have lived without much worry about their cancer because they cannot see or feel it. But we know it is there. If we stopped treatment the disease would relapse, probably within a year, two at the most. This “out of sight and mind” approach is even easier and safer today with the availability of rituximab. Maintenance rituximab is today’s CVP without the side effects. With an injection of rituximab every few months, the majority of patients can be kept clinically disease free. A recent randomized trial employing maintenance rituximab (4) even suggests a small effect on overall survival, but the heterogeneity of the patients and the disease make one eager to see follow-up durations longer than the 3 years reported in that study.

One lesson that we have learned from years of study of follicular lymphoma is that we can make it go away, but it almost always comes back. If we had a way to eradicate subclinical tumor burdens in a safe and effective way, we might be able to cure the disease. Rituximab may help a bit, but all evidence is that it is masking rather than eliminating disease. Patients still relapse after their treatment stops; the responses may last a year or two longer, but the disease still comes back.

An extremely appealing strategy for taking the next step toward cure of follicular lymphoma is inducing long-term antitumor immunity. The notion that one could equip host defenses to eliminate or control subclinical tumor burden is being hotly pursued. We know the potential power of immunity. An 80-year-old who was vaccinated against smallpox as a child remains immune to the virus; thus, immunity can be long lasting. The destructive capacity of the immune system is also clear; a single image of a wheelchair-bound person with rheumatoid arthritis is sufficient testimony. Can we harness that power and focus it against the tumor? Perhaps so.

Follicular lymphoma is a clonal B cell malignancy that expresses a unique antigen that is formed by the immunoglobulin light and heavy chains, which combine to bind to a foreign antigen. The antigen-binding site is a structural feature of each immunoglobulin that distinguishes it from other immunoglobulins, and it is called the idiotype. The idiotype of a particular clonal B cell lymphoma represents a tumor-specific antigen. Idiotype is a target of interest in human lymphoma primarily because of the work of Ron Levy at Stanford. Although the idea of using idiotype as a target for controlling B cell tumors originated in animal studies by Richard Lynch and his colleagues (5) and although some other investigators, notably Freda Stevenson, have made contributions to the field, Levy conceived of and pioneered the clinical approach and has made nearly all the technical developments that make it possible to identify and produce clinically useful amounts of tumor-derived idiotype-bearing molecules for use in people.

Levy invented the technique of rescue fusion to generate an immortal cell line that could produce gram quantities of the immunoglobulin expressed by a person’s lymphoma cells (6). He led the first clinical study using anti-idiotype antibody as passive serotherapy (7). He defined a number of features that undermined the success of passive serotherapy, including shedding of idiotype from the tumor and decreased tumor expression of idiotype. Along with a group from the National Cancer Institute (8), he and his colleagues also noted the spontaneous alteration of idiotype by the lymphoma cells (9).

Years of animal work followed to define the features of an effective approach to active immunotherapy using tumor idiotype as a vaccine [for example, (10)]. Then it was back to humans with a vaccine made of idiotype (Id) conjugated to the immunogenic protein keyhole limpet hemocyanin (KLH) given with an immunologic adjuvant (11). Half of the patients made a measurable immune response. Those who made an immune response had longer remissions, but this result was an association and not necessarily a reflection of cause and effect. The capacity to make an immune response to an antigen, rather than the specific response to the tumor antigen, could be the relevant biologic marker here.

One of Dr Levy’s scientific offspring, Larry Kwak, took the clinical development of idiotype vaccines a step further when he injected patients who were in a chemotherapy-induced remission with Id-KLH plus granulocyte–macrophage colony-stimulating factor (GM-CSF) (12). This approach induced cellular anti-idiotypic immunity in 19 of 20 patients, and in most of the patients the residual t(14;18)–bearing tumor cells were eliminated by the vaccine. This and other promising results from phase II trials (13) stimulated the initiation of three phase III studies comparing Id-KLH plus GM-CSF with either KLH or placebo, one sponsored by Genitope (affiliated with Levy), one by the National Cancer Institute (affiliated with Kwak), and one by Favrlle. Genitope announced in a recent press release that after interim analysis of the Genitope study (which is now closed to accrual) on July 27, 2006, the Data and Safety Monitoring Board recommended that the study continue, which suggests that there was no statistically significantdifference in progression-free survival between the arms.

Of course, the sequential evaluation of a new intervention from phase I to phase II to phase III is logical course for clinical development. But does this progression make sense for an intervention that is different in every patient who receives it? The experimental group in a phase III study of idiotype vaccination is not the typical experimental group of a phase III study of a new drug. We have known since the earliest report of idiotype-based immunotherapy that different idiotypes vary in their capacity to elicit protective immunity. In the original paper of Lynch et al. (5), MOPC 315 monoclonal antibody vaccination was much more effective at protecting vaccinated animals against MOPC 315 tumors than MOPC 460 antibody was in protecting against MOPC 460 tumors. Would you be able to judge a drug in phase III if every patient received a different dose? What if you had no way of knowing how much of the test drug the patient received or whether they received any at all? This problem struck Maurizio Bendandi, a scientific grandson of Levy through Kwak, and he set out to address the issue of idiotype vaccine efficacy in another way, a way that seems quite innovative and convincing to me. The results of his efforts are reported in this issue of the Journal (14).

One of the many lessons that we have learned about follicular lymphoma is that the first therapy achieves a higher response rate than the second, which achieves a higher response rate than the...
third, and so on. And first remissions are longer than second remissions, which are longer than third remissions, and so on (15).

The Bendandi group decided to assess the effect of idiotype vaccination by quantitating the duration of second remission in patients who had received an initial serious attempt at remission induction but who had relapsed. Patients on the study had relapsed from a combination chemotherapy–induced complete remission. They received a second course of combination chemotherapy and then were given Id-KLH vaccine. The median duration of second remissions in response to nearly any conventional-dose treatment regimen, even to repeated courses of the therapy that induced the initial remission, is about 13 months. Thus, the choice of the study design was the first innovation. Each patient would be his or her own control. Second remissions longer than first remissions would be an indication of therapeutic effect.

The second innovation was the use of multiple repeat exposures to the idiotype vaccine over a period of 2 years after completing chemotherapy. Patients received the vaccine monthly for 4 months, then received a boost 2 months later (at month 6), and then five additional boosts, one every 3 months. This approach is analogous to how maintenance rituximab is given, but I am unaware of any preclinical model evaluating multiple injections of a vaccine as a cancer therapy. Multiple injections of some antigens are required to reach protective levels of immunity (e.g., hepatitis B). Another value of vaccination is, as Levy showed, that it allows the generation of a broad range of host lymphocyte specificities that can recognize even the frequent point mutations in the idiotype that can occur over time in follicular lymphoma (16). However, I am not aware of data suggesting that 10 vaccinations provide a wider spectrum of lymphocyte specificities than three or four vaccinations. I do not know why Bendandi used multiple vaccinations, but it worked.

The results are remarkable. Of 25 patients who achieved a second chemotherapy-induced remission and were vaccinated with idiotype, 20 made an immune response to the vaccine and 5 did not respond to the vaccine. Among the 20 immunologic responders, the median duration of the second complete response has not been reached after nearly 3 years of follow-up (durations range from 20+ to 51+ months), and in every case, the second remissions have been longer than the initial remissions. By contrast, all five immunologic nonresponders have relapsed, and in every case their second remissions were shorter than their first. Long second remissions do not occur at this rate even after high-dose therapy and autologous hematopoietic stem cell transplantation.

Of course, longer follow-up will be revealing. Is the idiotype vaccine–induced immune response suppressing tumor cell growth on an ongoing basis (i.e., keeping it at a subclinical level) or has the tumor been eliminated? The persistence of responses beyond when an anti-idiotypic immune response can be measured may argue for elimination rather than suppression. Time will tell. Only a single immunologic responder has relapsed, and that patient had an altered idiotype at the time of relapse. It will be important to characterize the features of tumors from other responders as they relapse (if they do).

Three of the five immunologic nonresponders had received prior rituximab. Of the 10 immunologic responders who had received prior rituximab, seven made both humoral and cellular responses and three made only cellular responses. It is not clear whether rituximab adversely affects vaccine responsiveness. Is a humoral response important in the control of follicular lymphoma? The question needs to be addressed on a larger scale.

The Inoges et al. study (14) is not a randomized trial. But I find the data in the paper persuasive that idiotype vaccination is influencing the natural history of disease. If the observed remissions remain durable, the stage seems set for a head-to-head comparison between rituximab and idiotype vaccination as postremission therapy in patients who achieve an initial chemotherapy-induced complete remission. If that comparison reveals a clear winner based on a disease-free survival endpoint, it may be time to consider putting in the effort to conduct a major study assessing overall survival.

**REFERENCES**


