Idiotype vaccine therapy (BiovaxID) in follicular lymphoma in first complete remission: Phase III clinical trial results

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Background

- **Non-Hodgkin’s Lymphoma** (NHL) is the 6th most common type of cancer in the US. There will be approximately 65,980 new cases diagnosed in the US in 2009.

- Follicular Lymphoma (FL) is the 2nd most common type of NHL and accounts for 25% of all NHL. It is a B-cell derived neoplasm which expresses a specific idiotype maker on the surface of tumor cells.

- Although we now have aggressive chemotherapy and recent advances in therapy such as monoclonal antibodies like Rituxan for the treatment of NHL, there are still no curative treatment options for most patients with this disease. Advanced stage FL patients can have an indolent, but ultimately fatal clinical course, and the majority of patients die of cancer-related death within 7 years from diagnosis.

- Since the 1980’s, there has been much work done on development of a patient-specific follicular lymphoma (FL) vaccine and this work showed feasibility of these vaccines. The BiovaxID vaccine was developed during these studies and is composed of tumor specific immunogens that induce immunity against Id-bearing tumor cells, which allows this sparing of normal cells since they do not have these idiotype markers.

- The production of this vaccine utilizes a patient specific process to create a tailor-made cancer vaccine for an individual patient. Cells are harvested from patient’s LN biopsies and unique cancer markers or idiotypes are identified. The tumor cells are then fused with a mouse/human fusion partner to create a hybridoma that secretes the idiotype. The purified idiotype is conjugated to an immune stimulant such as KLH in this case. It is then given back to the patient with another immune stimulant such as GM-CSF in this case, and then vaccine then triggers an anti-Id immune response in the patient.

- In a previous NCI Phase II clinical trial, tumor-specific purified idiotype (Id) protein conjugated to keyhole limpet hemocyanin (KLH) administered with granulocyte-monocyte colony stimulating factor (GM-CSF) induced follicular lymphoma (FL)-specific immune responses and molecular remissions (Bendandi, et. al., Nat Med 1999). This trial formed the basis for the current study.

- The current trial is a prospective randomized double-blind placebo-controlled multicenter phase III study of patient-specific autologous tumor-derived Id vaccine compared to control group in advanced stage previously untreated FL patients.

Materials and Methods
Inclusion criteria:

- Patients with FL with monoclonal IgM or IgG.
- Grades 1, 2, or 3a.
- Stage III or IV or IIx.
- Chemotherapy-naïve.
- Patients with a lymph node adequate for vaccine production (>2cm).
- < 2 sites of previous radiation therapy.

Schema:

- Patient’s LN biopsy was used for generation of vaccine.
- All patients received PACE (prednisone, doxorubicin, cyclophosphamide, and etoposide) chemotherapy.
- Those patients achieving a complete response (CR) or complete response unconfirmed (CRu) after chemotherapy were stratified by International Prognostic Index risk group and randomized 2:1 to receive either vaccination with Id-KLH/GM-CSF or control (KLH/GM-CSF).
- Vaccine therapy began 6 months after randomization to allow for proper response assessment.

The primary objective of this study was to examine if the vaccine prolongs disease-free survival (DFS) compared to the control group. The secondary endpoint was to compare safety profiles, OS, and evaluate immunologic and molecular responses of the 2 groups.

The secondary objective was to examine and compare progression-free-survival (PFS), overall survival (OS), and toxicity data in the two groups.

The sample size required by the protocol was 563 patients (which assumed a 2/3 response to PACE) for an 80% power to detect differences between DFS in both arms.

An intent-to-treat (ITT) analysis was performed for all randomized patients and a modified-ITT (m-ITT) analysis was performed for all randomized patients who remained in remission with CR at time of vaccination.

The study was concluded in 2007 based on recommendations from the Data Monitor Committee due to adequate results with no safety concerns.

Results

- 234 patients who received PACE chemotherapy were enrolled on the study from 2000-2007, however only 177 (76%) patients achieved CR/CRu and were randomized. (57 patients were excluded from randomization based on failure to achieve CR or CRu)
- Of the 177 randomized patients, 117 maintained CR/CRu > 6 months per protocol requirement and then received at least one dose of vaccine, 55 relapsed before vaccination, 4 were vaccine manufacturing failures and 1 violated protocol.
- 76 patients received Id-KLH/GM-CSF and 41 pts received the KLH/GM-CSF for control.
- In the ITT analysis, comparing all randomized patients (not just those that were vaccinated), there was no statistically significant difference see between the 2 groups.
- However, the intent of the study was to look at the effect of the vaccination, so the modified-ITT analysis was used to determine efficacy. Patients who received > one vaccine dose constituted the modified intent-to-treat study population for determination of efficacy.
In the m-ITT analysis (n=117), the patient groups were well-balanced by demographics without statistically significant differences seen between the 2 groups.

- Differences in med OS were not yet reached at a median follow up of 56.6 months (95.4% in experimental group vs. 91.2% in the control group, p=non-significant).
- However, at a median follow-up of 56.6 months, median time to relapse after randomization for the experimental arm was 44.2 months versus 30.6 months for the control arm (p=0.045; HR=0.62).

- No serious adverse events were attributed to the experimental agent. No differences in Grade III/IV hematologic or non-hematologic toxicities were seen between the 2 groups and the vaccine was well-tolerated.
- The erythema and induration measurements performed to assess local injection site reactions were equally matched making this a truly blinded study.

Author's Conclusions

- Id vaccination after chemotherapy-induced remission of >6 mo prolongs remission duration in pts with FL.
- Compared to other phase III Id vaccine trials, the positive outcome of this trial may reflect application of Id vaccine in pts with CR/CRu or use of hybridomas to produce the Id vaccine.
  - It is thought that CR/CRu may be a prerequisite for achieving a benefit to this vaccine, since other trials where PRs were included were negative.

- This vaccine demonstrates a low toxicity profile and is safe to use in patients.
- The vaccine production is clinically applicable and can be reproduced.
- Future studies proposed by the authors are to complete genomic and immune response analyses on residual autologous tumor and blood samples collected during the study.
  - Another idea for future research also includes studying Id-booster vaccination schedules.
  - Additional studies of this patient-specific vaccine in FL pts pretreated with anti-CD20 antibody-containing chemotherapy are indicated.

Clinical/Scientific Implications

- Anti-idiotypic treatment for lymphoma provides a tempting target for novel therapies because of idiotypes are unique to tumor cells and not found on normal cells. This allows for better targeting and less toxicity to normal tissue.

- This trial represents a well-designed prospective randomized double-blind placebo-controlled multicenter phase III study, however its major limitation is its small sample size of n=117. The original goal of accrual of this study was much higher. The reasons for the long accrual period of the study and small numbers may be due to: unpopular chemotherapy regimen, 25% loss of patients who had failure to achieve CR, and another 25% loss of patients who had failure to maintain a CR. For this reason, the positive results of this trial can only be applied to the 50% that remained with CR.
- Despite this limitation, the trial did show a positive result in its modified-ITT to treat analysis of those patients were vaccinated after maintenance of CR after randomization, and the results are promising for those patients in the CR category.
- Other previous trials such as the Genitope and Favrille trials on Id-vaccine therapy had negative results for PFS on an ITT analysis. The difference between the current trial and these previous negative trials may be that those trials also included patients with partial responses. In essence, the study populations were inherently different. Furthermore, the previous trials used to molecular cloning to make the vaccine while this study used "rescue hybridization." This may account for the differences seen in the results.
• Although this study provides provocative results for vaccine therapy in FL patients, current management of lymphoma has included the use of Rituxan in the past few years. In light of this, one question that must be asked is: Is there a role of this vaccine in combination with Rituxan, or are the results of vaccine therapy superior to results with the use of Rituxan?
  
  • We may need to design future trials to compare this therapy with Rituxan or incorporate its used with Rituxan containing chemotherapy regimens.

• Another major question that arises from this study is: What is the ideal timing for delivery of vaccine? Could it be used before chemotherapy? Should it be given earlier while patients are still in CR and before they progress?

• The authors of this study have reported very promising results of vaccine therapy in FL, however many questions are still left unanswered which are mentioned above. The principles and the findings of this study should be used to redesign strategies for the use of vaccines along with therapies currently being used to treat FL in future studies.

See Patient Summary