Notes on August 19, 2004 Visit to Dr. Bendandi by Andrew Michael

Introduction

This note summarizes our visit to Dr. Bendandi in Pamplona on August 19, 2004. This was an information-seeking visit to see if we would want to return there for an anti-idiotype vaccine if my follicular non-Hodgkin's Lymphoma progresses before this treatment is available in the US. In the US, it is the subject of three phase III trials sponsored by Genitope, Favrille, and the National Cancer Institute. The latter two are currently accepting patients while the Genitope trial has closed. If you are not familiar with the anti-idiotype vaccine therapy for non-Hodgkin's Lymphoma I recommend that you start your research by visiting the web page about this at http://www.lymphomation.org/vaccines.htm . From there you can find references to many articles about this treatment for further reading. Simply put it is an attempt to expose ones immune system to a protein found on the cancerous cells in such a way that an immune response is developed and ones own immune system begins to fight against the lymphoma.

The trip was an overnight from London during a family vacation there. So, it was quite brief but allowed us to explore the area, how to get around, and (most importantly) to get to know Dr. Bendandi. This post will cover our visit with Dr. Bendandi and then the logistics of our trip. The technical parts of this post were reviewed by Dr. Bendandi and it is being posted with his permission. However, he did not review the rest of it (including my opinions about him!). In the interest of "truth in advertising" I have marked the beginning and end of the sections he reviewed.

These notes are based on my trip along with my wife Stephanie. However, we were greatly helped by advice from fellow patient Fernando Castanheira who is further along this road than I am. I am also very grateful to Dr. Bendandi for taking a substantial amount of time to meet with us and has graciously answered many questions via email.

These notes assume a familiarity with follicular non-Hodgkin's Lymphoma and the tests and treatments used during its treatment including some knowledge of the vaccine process. If terms such as CHOP, CVP, PACE, PET, MRI, CT, KLH, hybridoma and transformation are not familiar to you, please research them on the site http://www.lymphomation.org.

Dr. Bendandi and Vaccine Treatment in Pamplona

As noted in Neil Ruzic's book "Racing to a Cure", Dr. Bendandi is quite religious and I found that he matches this with a passion for the power of the vaccine to help those of us with indolent lymphomas. As a scientist, I also judged that he has very clear opinions on various treatment options and clearly separates those that can be backed up by statistically significant evidence and those that are opinion. We spent about 2.5 hours discussing lymphoma and vaccines and overall I found him to be a very creative and

rigorous scientist as well as a personable, caring, and funny person. I would be happy to have him treat me if it comes to that.

The other part of being treated in Pamplona is having surgery in the University of Navarra hospital (The Clinica Universetaria). We didn't have an extensive tour of the hospital but did take a walk through as Dr. Bendandi led us from the oncology reception area to his office and it looks like most other hospitals I have been in. It was actually quite complicated getting to his office due to intervening locked psychiatric wards and construction in the way and so we got to see a fair bit. They are also in the process of completing a new wing to the hospital and his group will be moving into that wing. Therefore, what I saw will be out of date soon and I won't try to give you directions to his office.

[Note: part reviewed by Dr. Bendandi starts here.]

Dr. Bendandi published a review article in Expert Reviews of Vacines in April, 2004 (citation is Expert Rev Vaccines. 2004 Apr;3(2):163-70. PMID: 15056042). So, that paper is a good resource for learning about his opinions. Below I will summarize the process of getting vaccinated by him as a paying customer.

He is also running clinical trials. Participation in those is open to those in first relapse, regardless of prior exposure to an anti-id vaccine or KLH. One of the issues I discussed with him, as it concerns participation in the various US trials, is the effect of prior exposure to KLH before receiving an actual vaccine. His opinion is that such prior exposure will not be a disadvantage and may be an advantage because the immune system will be pre-trained to treat KLH as a foreign protein. Similarly, while there is some evidence that prior treatment with chemotherapy could limit the effectiveness of the vaccine he has had positive experience vaccinating patients in first relapse. Again, this would bode well for patients in the control arms of the US trials. For information on participation in his trials, please contact him directly.

Up to the end of August, 2004, 30 patients have undergone a biopsy for vaccine treatment under Dr. Bendandi's supervision. Fifteen patients have either begun or completed the vaccination process, 10 will start vaccinations once either they complete chemotherapy or the vaccine is completed, and there were 5 failures to produce the vaccine.

Here is what I would go through if I progress before the vaccine is available in the US. When I need treatment I would contact Dr. Bendandi who will put me in contact with a surgeon to schedule an excisional biopsy. They want a 2cm x 2cm by 2cm node which provides enough material for up to 5 attempts at the hybridoma process. He is also experimenting with recombinant methods of producing the vaccine but does not know whether this will provide an equally effective vaccine although it does allow one to produce more doses for a longer program of boosters. He simply feels that the recombinant method has not had as much testing as the hybridoma method at this point.

Payment for the surgery is done with the hospital and depends on the nature of the surgery. Some nodes, such as the inguinal ones I have, can be excised under local anesthetic as outpatient surgery or may require an overnight stay if the surgery is done late in the day. But, others may require general anesthetic and a day or so of inpatient recovery.

Current payment for the attempt at producing the vaccine with the hybridoma method is $5,000. He would also make an attempt with the gene replication method, but there is no additional charge for that. He noted that current exchange rates make it a bargain that they have priced it in US dollars. The success rate at producing a vaccine with the hybridoma method is around 85%.

Once I have recovered from surgery, I would return to the US for chemotherapy. His strong preference is to treat with CHOP in order to have the highest probability of obtaining a complete response (CR). We discussed what one would then use in case of transformation and his opinion is to either use CHOP as the initial CHOP will not reach the dose-limiting levels or to replace the doxorubicin with mitoxantrone for treatment with CNOP. He concedes that the effectiveness of CNOP with respect to CHOP has not been tested for transformed disease but also noted that even CHOP has limited effectiveness in treating transformed disease. Overall, I think his attitude can be summarized as doing what it takes to get the best response from the vaccine. He doesn't think this attempt should be made less effective due to worries about transformation because transformation may not happen anyway (he cited rates around 30% for transformation) and it is hard to treat no matter what. Other options he cited for transformed disease were Zevalin, Bexxar, and transplants.

He also dislikes using Rituxan and Fludarabine as pre-vaccine treatments due to their effects on healthy b-cells and t-cells respectively. It takes the immune system 6 to 12 months to recover from these effects and that could be a long time to wait before vaccinating.

We discussed the option of starting with CVP and then switching to CHOP if the CVP isn't sufficiently effective. He just thinks it is wiser to use the CHOP immediately and get to CR as quickly as possible. My oncologist's preference is CVP and so this is an issue that we will need to hammer out when the time comes. He is willing to treat paying customers like myself as our oncologists prefer but for the trial participants he uses CHOP.

The work he did at the National Cancer Institute (Bendandi et al., 1999, Nature Medicine, v. 5, pp. 1171-1177) used PACE as the pre-vaccine chemotherapy and PACE is also being used in the NCI vaccine trials. Without a trial formally comparing the CR rate PACE to CHOP, his opinion is that they have a similar ability to produce a CR and is using the more commonly used CHOP for his work.

After finishing chemotherapy, and assuming that the vaccine was successfully produced, I would return to Pamplona for a standard vaccine schedule of vaccine and GM-CSF on

day one, followed by GM-CSF alone on the following three days. I would only need to be in Pamplona for the first day and then could self-administer the GM-CSF on subsequent days. This cycle would be repeated monthly for at least five months with regular testing for the immune response to the vaccine. If an immune response is found, then less frequent boosters would be scheduled as long as there is a supply of vaccine available. This could be a long time if the gene replication method works in addition to the hybridoma method. The cost for the vaccination series, regardless of length as long as they make at least 5 doses, is $10,000.

And then we would see what happens.

We also discussed watch and wait protocols a bit. His preference is for CT scans and physical exams on a 6-month schedule. He doesn't think blood tests are particularly useful during watch and wait and definitely felt that the bimonthly chest x-rays I have been getting are excessive. He doesn't think that the radiation dose from CT-scans is a problem and prefers CT-scans to MRIs. He uses PET scans to look for residual amounts of disease after treatment to check for CR and is quite proud that the University of Navarra had the first PET machine in Spain and so has the expertise and experience needed to analyze low-grade lymphoma.

Concluding Thoughts

Overall, I am quite impressed with Dr. Bendandi as both a thoughtful doctor and scientist. As new non-toxic treatments become available and may have revolutionary impacts on the treatment of our disease, many of us are concerned with the use of conventional trials. Dr. Bendandi not only provides a source for the vaccine outside of the US but also shares our concerns about trial design. Over the years to come, I expect that he will be an important member of the lymphoma research community and a friend to lymphoma patients everywhere.

Currently he receives about an email per day from patients in the US and gets about one new US patient each month. If you are interested in either his clinical trials or paying for treatment, I recommend sending him an email (mbendandi@unav.es) explaining your situation. I should note that when I first contacted him, he would have suggested that I enter the Genitope phase III trial but has been willing to take me as a patient based on Dr. Levy's suggestion that I watch and wait instead of entering the Genitope trial. So, he does treat every person and situation individually and thus you really need to contact him to see what he suggests for you.

[Note: part reviewed by Dr. Bendandi ends here.]

Logistics

As we were in London before and after visiting Bendandi in Pamplona, we flew on EasyJet (www.easyjet.com) from London to Bilbao and then drove from Bilbao to Pamplona after visiting the Bilbao Guggenheim (an excellent reason for taking this

route). The car rental was done through Alamo which we reserved through Yahoo (travel.yahoo.com). Budget may be cheaper but was out of cars and Europacar has a special deal of some sort with EasyJet but didn't have a good rate for us. Driving from city to city was quite easy as the roads are well signed. Driving in the cities is harder as the street signs are almost impossible to read while driving.

Another route to Pamplona (especially if you are coming from further away) is to fly to Madrid and then take a connecting flight to Pamplona.

In Pamplona we stayed at the Blanca de Navarra which has the advantage of being about a block from the clinic. We had reserved a twin room through Yahoo but were given a nice suite for about 70 Euros a night. This is a simple hotel with a restaurant but no pool or exercise rooms. There may be wireless internet now, but we didn't have our laptop with us to try it out. Another hotel recommended by Dr. Bendandi is the Iruna Park which has more facilities but is further from the clinic. If we return, we may look for someplace with a kitchenette.

The reason for wanting a kitchenette is that while Spain is reputed to have great food, this should be qualified as great food unless you are a vegetarian. We had a lot of trouble finding vegetarian food in this region especially on a quick trip with little time to look around.

Fortunately, Fernando has used such a place. He says, "for the second trip (biopsy) I flew from New York to Madrid, connected on a flight to Pamplona. We stayed at an ApartHotel which is a nice small apartment with kitchen and the works. There are a couple of places like this we stayed at this one: Apartamentos Mirasierra, www.atmirasierra.com, 948-288-800. If you mentioned the Clinica Universetaria they will give you a discount. We paid 80euros/night. It's about a 15 minute walk or 5 minute bus ride to the hospital and we also used taxis to get around town."

Good maps and guidebooks: for regional driving the Michelin Regional Pais Vasco/Euskadi, Navarra, La Rioja map (#573) was very good. We had trouble finding a good map of Pamplona in the states but got one at the hospital's book and gift shop. It is the Pamplona Plano Callejero. They also had a good guidebook to the city called, "Pamplona Short Guide." Both the map and the guidebook are published by the city government (http://www.pamplona.net). An online version of the map is at http://www.pamplona.net/mapaweb/mapaweb1.htm and then look for Plano Callejero. The hotel provided a book called "Routes from Pamplona, 10 itineraries to discover Navarre" which details driving trips into the surrounding countryside. Lot's of pictures of great geology in that book and so we would definitely want to do some of those if we return. This book is published by the Association of Hotels of Pamplona (http://www.hotelespamplona.com) and while the copy in our room was in Spanish the front desk gave us one in English. A general guidebook to the area is Bilbao and the Basque Lands by Facaros and Pauls, published by Cadogan Guides. We chose that one because it covered the Guggenheim Museum in Bilbao.

After visiting Dr. Bendandi, we did have time to drive to the central part of Pamplona and walked around the area where the running of the bulls is done as well as many of the areas plazas and parks. It is certainly someplace worth spending some more time.

Photos

This is a picture of the main entrance of the Clinica Universitaria.

This is a view of the hospital (white building in the top center) from the Hotel Blanca de Navarre. The crane in front of the Clinica is working on the new hospital wing.

This is a view of the hotel from the corner outside of the hospital. It really is very close. Also, the sign at the top is brightly lit at night and was a very welcome sign when we arrived around midnight! Also note the universal sign of a university hospital: someone wearing their white lab coat.