Options for Patients with Advanced Stage Low Grade Follicular NHL

By Dr. Andrew Croaker

Wait and See Approach

With nearly all forms of cancer, once detection has occurred and disease staging been completed, patients are quickly commenced on treatment in the hope of obtaining the best possible outcome. In most cancers, time works against the patient. Delaying treatment allows the disease to progress, treatment becomes less successful, and death more likely. One wouldn't, for example, recommend a 'wait and see' approach to a patient recently diagnosed with breast cancer. Such delays would allow the cancer to spread to other parts of the body and reduce survival prospects.

Such a 'wait and see' approach has however been recommended by some doctors for low grade NHL. At first the idea sounds a little crazy. Instead of jumping into treatment you get your haematologist to monitor your disease over a period of months and in many cases years. Provided you do not become unwell and the disease isn't progressing rapidly you wait and withold treatment.

As patients, this can be a very difficult idea to understand. Time and time again we have been told how deadly cancer is and how important it is to hit the disease hard and fast. Why then is the wait and see approach an option for advanced low grade NHL?

The main reason doctors began the 'wait and see' recommendation in the 1970's was because they had found that early intensive treatment of advanced indolent NHL did not improve patient survival nor yield durable remissions. No matter what treatment they tried, nor how soon after diagnosis they used it, patients were no better off. They were not cured and lived for the same length of time as patients who had not been started on treatment straight away. Unlike other cancers, there was no advantage to be gained by patients in the early aggressive treatment of advanced low grade NHL with chemotherapy or radiotherapy (although one recently published trial casts doubt on this whole premise).

With no reason to recommend these treatments in symptom free patients and a desire to avoid toxic therapies if not clinically warranted, a number of patients opted for the 'wait and see' approach. One paper submitted in1984 reported the outcomes for a group of 83 initially untreated low grade NHL patients. The average age of patients was 57 years at diagnosis, 77% had Stage IV disease and 94% were symptom free.

This group of patients were observed with initial treatment being deferred. The criteria for initiating treatment being disease progression as assessed by the rate of growth and absolute bulk of measurable disease and the development of systemic symptoms, anaemia or thrombocytopenia. The other indication being the development of new disease in threatening extranodal sites eg. near the eye.

In this study it was found that due to disease progression, patients had to start treatment on average three years after they were diagnosed. An interesting feature was that the treatment free period seemed to vary depending upon the type of follicular lymphoma one had. Those with follicular mixed small cleaved cell and large cell lymphoma needed to start treatment on average after 16.5 months; those with follicular small cleaved-cell lymphoma after 48 months; and those with small lymphocytic lymphoma after 72 months. Although the number of people enrolled in the study was small, it does suggest that ones follicular lymphoma subtype gives some indication as to how rapidly the disease process may progress. Of course these are only average figures and individuals with a particular subtype could progress in a vastly different manner to the patients enrolled in this study.

Two important topics to discuss in relation to the 'Watch and Wait Approach' are Spontaneous Regressions and Transformations. One prays for a spontaneous regression, and hopes they don't undergo transformation.

A spontaneous regression is where a cancer, not under the influence of any treatment, either totally goes away (complete) or reduces in size/volume (partial). It was found that 7% of patients had a complete spontaneous regression, while 15% underwent a partial regression. The average time from diagnosis to a spontaneous regression was eight months. The process usually taking a few months to run its course. Almost one third of patients with follicular, small cleaved cell lymphoma had a spontaneous regression, for those with a partial regression the average duration was 15 months. Of those who underwent regression only about 50% had subsequent progression of their disease. It is currently unclear why some people undergo a spontaneous regression. Probably (although this is pure conjecture), it is because the immune system for some reason becomes able to recognise and target the lymphoma cells. One interesting finding is that one of the patients had a complete spontaneous regression after a viral illness.

Transformation on the other hand is where the lymphoma cells change from a low grade to a more aggressive form. This usually has a significant detrimental impact on survival. When comparing the rate of transformation in 'wait and see' patients and those immediately commenced on treatment they were about the same for both groups (19 vs 23% respectively). Some had theorised that the damaging effect of treatment with chemo and radiotherapy would increase the rate of transformation in the protocol group. As you can see the rates are about the same. The average time from diagnosis when transformation occurred, was also similar for the two groups (57 months vs 54 months). Transformation occurring from 6 to 185 months after diagnosis.

Some people are happy to 'Watch and Wait'. They feel their best chance of being cured is during their first course of treatment. They believe there is currently no proven cure for indolent NHL, and any potentially curative treatments eg. vaccines are still in their infancy. Thus in a sense, patients who decide to wait are setting up a contest between father time and medical progress/treatment availability. If their disease progresses slowly they may win the gamble. They may be able to delay treatment until a clear winner has been found or until a treatment they feel can be curative is available outside the placebo trial roulette wheel. If on the other hand the disease progresses and they are forced into treatment, then a choice must be made on the data at hand.

Watching and waiting is not everyone's psychological cup of tea. The thought of sitting there doing nothing while a cancer slowly progresses through your body is abhorent to many. One can't help but to frequently feel their lymph nodes several times an hour just to check that they haven't miraculously vanished or gotten any bigger. By the end of the day you are alarmed to find they have actually enlarged and are now tender. After a few panicked moments dreading you have transformed you realise that this is probably because you've been poking them all day long. One of the best pieces of advise I was ever given by a haematologist was to staple-gun my hands to my knees and stop traumatising myself.

The main backers of the wait and see approach were based at Stanford University. This is a legitimate treatment option for patients although with new evidence to hand I feel there is a strong argument to be made for early aggressive treatment of advanced indolent/ follicular NHL.

While reviewing the literature I have found several potentially curable treatments for Follicular NHL. These are listed below with a brief summary of the article the information was drawn from. I have avoided discussing stem cell transplantation both autologous (from self) and allogeneic (from sibling). This is due to several factors one being time constraints, the other being it's a highly involved area where expert advice from several sources should be sought. Thus the following text does not include all possible options available to patients and should be viewed in this light. As a disclaimer it is information which I found useful and hope it will help others to make appropriate informed decisions.

Combined Therapy in Advanced Stages (III and IV) of Follicular Lymphoma Increases the Possibility of Cure: Results of a Large Controlled Clinical Trial. European Journal of Haematology 2002: 68: 144-149. Aviles et al.

This study I feel raises serious doubts over the idea that Follicular NHL is incurable with currently available treatments. The two great strengths of the study are the large number of subjects (469) and the follow up time period (average 13.6 years range 7.3-21.6 years).

To summarise their study design 769 patients were given a variety of anthracyclin based chemotherapy regimes. Those achieving a complete response (disappearance of all detectable clinical and radiological evidence of disease/ disappearance of all disease related symptoms/ and the normalisation of biochemical abnormalities assignable to lymphoma) were divided into a control group who received no further therapy and a treatment arm who received adjuvant radiotherapy.

Of the 769 patients initially enrolled, 469 attained a CR and continued in the trial. The number of patients who received adjuvant radiotherapy were 251; the control group receiving no radiotherapy numbered 218.

Of the 218 patients in the control group 91 remain in their first CR. Of the 251 patients receiving adjuvant radiotherapy 176 remain in their first CR. This really is an impressive result.

Control Group: Event Free Survival 41% Overall Survival 71%
Adjuvant Chemotherapy: Event Free Survival 68% Overall Survival 89%

The follow up period again 13.6 years (range 7.3-21.6 years).

One problem I had with the paper was some confusion over whether the patients all had bulky disease and what they classified this as. If all patients had bulky disease which is usually associated with a worse prognosis then the results are even more impressive and the EFS could possibly be higher if this treatment was used in patients who had Stage III/IV disease that wasn't bulky.

The other issue is several different chemotherapy regimes were used making the results a little difficult to tease out including one group who received both COPP and interferon.

The other potential problem some specialists may have is that the research was conducted in Mexico. The results I feel speak for themselves but some may have a problem with this.

At the very least this result should trigger some large Phase III trials in the US. Possibly also incorporating Rituximab to see if the EFS and OS results can be improved on. As a patient it is great to see a study where the oft told story of frequent recurrence and poor prognosis has been challenged with currently available treatment.

If it is possible to cure Follicular NHL it would make the wait and see strategy less rational. By waiting the tumour burden increases possibly making it more difficult to achieve that important first CR. The possible risks of pursuing this course of action are that there may be an increased toxicity profile including secondary malignancies. But in this study only 4 patients developed a haematological malignancy following treatment and only 2% developed cardiac toxicity secondary to treatment. Thus the potential gain of aggressive combined intervention appears great while the risks appear relatively small in this study.

For a specialist to feel comfortable advising patients to take this course you would really want another study reproducing these findings. Unfortunately that will be some years away and most patients currently with disease won't be able to wait long enough to find out.

There are other studies out there suggesting potential cure with currently available therapy.

Chemotherapy induced Molecular Remissions with Long Term Follow Up

The Clinical Significance of Molecular Response in Indolent Follicular Lymphomas. Guillermo, A; Lee, M et al. Blood April 1998.

There were 192 subjects in this study 22% had Stage I-II disease; 14.5% had Stage III; 63.5% had Stage IV disease. Of the 123 patients with stage IV disease 87 cases were treated with (ATT) Alternating Triple Therapy, 24 were treated with FMD (Fludarabine, Mitoxantrone and Dexamethasone) and 12 patients who refused investigational treatments were given CHOP. Interferon maintenance was used after completion of chemotherapy in all those cases. Patients with Stage III disease were treated with ATT in 13 cases or with CHOP plus radiotherapy in 15. Patients with early stages (I or II) received radiotherapy (6 cases) or COP-bleo plus involved field radiotherapy (35 cases).

Molecular Remission within the first year and a normal pre-treatment B2-M are important prognostic predictors for Failure Free Survival. 80% of these patients are projected to be alive and in complete remission at 5 years. This group with excellent prognosis represents approximately one half of all the FL cases in this study. “Longer follow-up will be necessary to determine if a significant proportion of those patients are cured”.

Clinical CR was attained in 173 patients (90.6%), PR in 17 patients (8.9%) and 1 (0.5%) did not respond. Failure Free Survival 89.1% and 62.5% at 2 and 5 years from diagnosis. Stage IV patients receiving the FMD combination presented a higher molecular response rate at 6 to 8 months than those treated with ATT (82% v 49%).

In a separate analysis of the association between pre-treatment patient characteristics and FFS (including age, sex, histologic subtype, performance status, B-symptoms, bulky disease, extra-nodal involvement, bone marrow infiltration, Ann Arbor stage, serum LDH, serum B2-M and treatment. It was determined that serum LDH and B2-M values were the two factors most closely associated with FFS outcomes. (although other studies have suggested that B2-M levels don’t give prognostic information). Also there was a substantial failure-free advantage for patients with evidence of molecular response within the first year of therapy.

This paper was published in 1998. If anyone has any follow-up data so we can determine what proportion of patients remain in CR it would be appreciated.

So summarising this first section we have one paper showing patients can be cured with anthracyclin based chemotherapy and that the cure rate is increased by use of adjuvant radiotherapy. A second paper shows that some patients may be cured by a fludarabine chemotherapy regime.

CHOP plus Mabthera

Firstly we should discuss the constituents of this treatment combination.

CHOP: not a vegetarians nightmare, this is actually a chemotherapy combination.
Cyclophosphamide 750mg/m2 IV (intravenously) on day 1.
Vincristine 1.4mg/m2 on day 1.
Doxorubicin 50mg/m2 on day 1.
Prednisone 100mg/day orally on days 1 to 5.

Mabthera (rituximab): A monoclonal antibody which targets the CD 20 molecule found on a majority of lymphoma cells in patients with low grade NHL.

ASH (American Society of Haematology) December 2001.
Abstract 2519: Progression free survival after six years (median) follow-up of the first clinical trial of RITUXIMAB/CHOP chemoimmunotherapy.

In this phase II trial of 40 patients 83% had stage III/ IV disease at diagnosis.
31 had never been previously treated, 9 had.
They were given 6 cycles of CHOP.
Rituximab: 2 doses were given both at the beginning and end of therapy as well as single doses before the 3rd and 5th cycles of CHOP.

Of 40 patients registered 38 were treated (two received no therapy) and 35 completed all therapy.
All patients treated responded (58% CR 42% PR) and the overall response rate in patients who completed all therapy was 100% (63% CR 37% PR).
Median duration of response is 63.6+ months with median Progression Free Survival not reached.
Twenty one patients are still in remission at 46.8+ and up to 86.3+ months. Seven of eight Bcl-2 positive patients converted to PCR-negativity in blood and marrow (molecular complete remissions).
Of these 7 patients, 6 remain in CR and 4 remain PCR-negative. Naïve and previously tr eated patients had similar demographics with a longer time till progression for the naïve patients.

Comments from ASH: " This study is a follow-up of the first clinical trial of rituximab in combination with CHOP chemotherapy in indolent lymphoma. These latest data reveal that over 50% of patients have not progressed during a median follow-up period of over 5 years. This is highly encouraging and raises the hope of this regimen providing curative therapy in some patients. Confirmation of these results is now required in larger randomised trials. To date there has never been a curative therapy for advanced indolent non-Hodgkins lymphoma". This I feel is incorrect given the results in the articles listed previously. We must remember that some groups would love us to believe that Follicular Lymphoma is incurable and that their expensive drug offers patients the best hope. After only 5 years of follow up it is a little premature to be mentioning the word cured. The results are however encouraging. It would be nice to have a break down so we can see how many of those still in remission are stage III/IV and how many are stage II; how many still in remission had not been previously treated and how many had.

Other CHOP/Rituximab Studies

Abstract 2528: Monitoring of Minimal Residual Disease after CHOP and Rituximab in previously untreated Follicular Lymphoma Patients.

At diagnosis, the presence of Bcl-2/IgH positive cells in the peripheral blood and/or bone marrow was demonstrated in all 128 patients by PCR analysis. Patients who after CHOP were in clinical complete (CR) remission or partial remission (PR), but persistently PCR +ve were eligible for Rituximab (375mg/sqm intravenously, weekly x 4) administration. After CHOP, the clinical response was a CR in 57% of cases, a PR in 37% and no response NR in 6%. At this stage, patients proving PCR negative (41 patients) or failing to achieve a clinical response (8 patients) were excluded from Rituximab treatment. Seventy seven patients received Rituximab and entered the Minimal Residual Disease follow-up program. At the first scheduled molecular follow-up (+12 weeks) 59% of patients were PCR negative in the bone marrow and blood, and a further increase of this response was documented at the second control (+28 weeks) when 74% proved PCR negative. At the last molecular follow-up 62% of the patients were still PCR negative.

For patients treated with Rituximab, a durable PCR negative status was associated with a better clinical outcome since the freedom from recurrence at three years was 57% as compared to 20% in those patients who never achieved or lost their PCR negative status. The failure free response of patients who achieved a PCR negative status at the end of CHOP was 52%. This confirmed the positive correlation between molecular and clinical response.

Abstract 3500: A Randomised Trial of Fludarabine and Mitoxantrone Plus Rituximab versus CHOP plus Rituximab as first-line treatment in patients with Follicular Lymphoma.

Patients were randomised to receive either FM (Fludarabine 25mg/m2/day IV on days 1 to 5 and Mitoxantrone 10mg/m2 IV on day 1) or CHOP (as previously described). In both arms, patients were assigned to receive 6 cycles of chemotherapy. Thereafter, to be eligible for Rituximab treatment they had to remain PCR positive in the BM and/or PB in two molecular analyses performed 4 and 6 weeks after the sixth cycle. These patients received four weekly IV of Rituximab.

At the end of chemotherapy the response rates for the FM arm were CR 64%/ PR 31%/ NR 5. The response rates for the CHOP arm were CR 42%/ PR 28%/ NR 9%. The molecular assessment revealed a PCR negative state in 34% of the FM arm and 10% in the CHOP arm. After Rituximab courses, the molecular evaluation documented the clearance in 71% and 44% for FM and CHOP subsets.

Summary.

CHOP plus Rituximab may be curative in a proportion of patients. Surprisingly some patients achieve molecular remissions following CHOP alone. I would not have thought they were cured as most haematologists feel the disease is currently incurable and CHOP chemotherapy has been around for a long time. Although one of my patients has been in remission for 10 years following CHOP with Low Grade NHL I think this must be the exception rather than the rule.

As seen in the first abstract a significant proportion of patients who became PCR negative later reverted. Thus attaining a PCR negative status does not mean you are out of the woods. It does improve your chances of prolonged disease free survival however.

If CHOP+ Rituximab does prove to be curative for a proportion of patients it does seem that FM chemotherapy + Rituximab should give an even higher cure rate based on the increased numbers obtaining molecular remission. Fludarabine does affect T cells and may reduce the effectiveness of any post treatment vaccine although I have no data to back this statement. Also Fludarabine is often used as salvage chemotherapy prior to stem cell transplantation. If you've already used it and the lymphoma recurs it may reduce your chances of successful autologous or allogeneic stem cell transplantation. This is pure speculation on my part, if anyone has any articles which blow this theory out of the water please email them to myself.

IMMUNOTHERAPY

Also known as vaccine therapy, basically this form of treatment uses a patients' own immune system to target and destroy cancer cells. There have been several different approaches to generating this response in cancer patients. We will explore each of them in moderate detail and assess their clinical effectiveness. First though it would probably be useful to discuss the immune system and how it works.

The first thing to understand is that the body's immune system is not designed to aggressively fight cancer. During embryological development, when the body is selecting which immune cells to keep and which to discard, it screens them to determine those which target our own tissues. This makes sense, you would not want immune cells running around your system which attack your own cells. Thus those immune cells which target proteins used by your own body are destroyed.

Cancer occurs basically in one of two ways. It is due to cells either uncontrollably rapidly dividing or failing to die at the appropriate time. Follicular Lymphoma is caused by mature B cells, failing to die (apoptose) at the appropriate time. Thus they accumulate and crowd out normal cells. When they do this in your bone marrow you start losing the ability to manufacture blood. You get anaemic (low haemoglobin level/ red blood cell count), thrombocytopaenic (low platelet count) and can have a reduction in functioning normal white blood cells predisposing you to infections. When the cancer cell accumulation occurs in lymph nodes they become enlarged and swollen, when in other sites they begin to disrupt that tissues normal functioning. All the time the cancer cells are doing these dastardly deeds, the immune system to a large extent is passively watching it happen. Because cancer cells have arisen from our own cells, there are no immune cells in our body specifically designed to target and destroy them.

Hang on a minute some are probably arguing. What about natural killer cells and tumour infiltrating lymphocytes. Natural killer cells are cells that circulate through the body and destroy abnormal cells. In fact most people have probably had several malignant cells form in their body over the course of their lifetime from a variety of different tissues. These however have been detected by circulating natural killer cells and destroyed before they can form a cancerous lesion. Yes, natural killer cells are an important defence against the formation of cancer, but for some reason in some individuals the malignant cells win the microscopic battle taking place and cancer ensues. Natural killer cells are important and currently there are studies underway trying to boost their numbers and level of activation.

Some may feel because of the failure of our immune system to prevent and combat cancer, it's a bit of a light-weight loser. One only has to see how our body deals with a foreign invader to see that this definitely isn't the case. Our immune system when activated is an incredibly powerful force, which has successfully protected humans from the hordes of nasties in our environment for eons. The goal of immunotherapy is to generate an immune response to specific cancer proteins and the cancer cells which contain them that is similar to our bodies response to external pathogens/ antigens.

So what usually happens when our body is exposed to a foreign pathogen or antigen. Lets take a bacteria, say staphlyococcus aureus (golden staph as its known in the community) as an example. You have a cut on your knee and a bunch of golden staph bugs have gotten into the wound. What defences does our body employ to eliminate this invader from our system?

Well the immune system is composed of several elements. Keeping it simple, there is a non-specific immune response, which can target a whole range of different antigens. I liken it to a guard dog, it mauls anything that jumps over the fence and breaks into your body. There is also a smart immune response, which powerfully targets a specific/unique antigen. I liken this arm of the immune system to a sniper/ assassin. It has one target and one target only that it can take out and it does so with ruthless efficiency. If the thing jumping over the fence isn't the specific target it has been trained to kill it does nothing. The body has literally millions of different snipers each one trained to kill a different/ unique antigen. Thus to overcome the bodies defences a bacteria must defeat or evade both the guard dog and the sniper. Not suprisingly this rarely occurs. Considering the microbe rich environment we live in, the relative rarity of infection is a testimony to the strength of the immune system.

Thus the trick with immunotherapy is to send the snipers back to boot camp and train them to recognise the cancer cells as an enemy. The first lymphoma vaccine we will examine is:

IDIOTYPE-KLH + GM-CSF vaccine

Idiotype: the unique tumour specific variable region located in the immunoglobulin molecule (antibody) which is present on the surface of follicle cell lymphoma cells. Every lymphoma cell in a patient is coated in this identical immunoglobulin. Thus it presents an excellent target for immunotherapy. Idiotype in this vaccine, is created by fusing a lymphoma cell to a mouse cell. This combination is termed a hybridoma. Hybridoma cells which secrete antibody identical to the tumour specimen are selected and their products filtered. This filtered product is the unique idiotype or specific immunoglobulin molecule found on every B lymphoma cancer cell in that patients body.

KLH (Keyhole Limpet Hemocyanin): this is the respiratory protein of the keyhole limpet a type of sea slug. The chemical is a hollow cylinder with two rings located close to both ends which move slightly together upon oxygenation. So what does a sea slugs respiratory protein have to do with a cancer vaccine. Well for some reason researchers were looking for molecules that stimulated the immune system. They found that KLH triggered a huge immune response. From this they theorised that to bind the idiotype to the larger KLH molecule may, as well as triggering an immune response to KLH, trigger one to the idiotype as well. They were right.

In 1994 Jennemann et al were interested to see if KLH had to be bound or conjugated to a tumour antigen for it to trigger an immune response. They had mice they injected with either conjugated KLH and tumour antigen or a mixture of KLH and tumour antigen unconjugated. They found that only those who were given conjugated KLH-tumour antigen developed an immune response. It seems that the bodies antigen processing/presenting cells known as dendritic cells will ignore idiotype unless it is bound to KLH. When they absorb the KLH and idiotype molecule and break it down into sections to present to the immune system they are tricked into thinking the idiotype is a foreign antigen and thus recruit immune cells to combat it.

GM-CSF: Granulocyte Monocyte Colony Stimulating Factor. This cytokine chemical messenger is used as an adjuvant meaning it boosts the immune response to the KLH-idiotype. GM-CSF attracts dendritic cells into the region the KLH-idiotype has been injected. With more dendritic cells, a greater number of T and B cells which target idiotype are recruited, generating a greater anti-tumour response.

So how effective is the Idiotype-KLH+ GM-CSF vaccine?

Study 1: Complete Molecular Remissions induced by patient-specific vaccination plus granulocyte-monocyte colony-stimulating factor against lymphoma. Bendandi, M; Kwak, L. Nature Medicine 1999.

Twenty patients with Stage III (15%) and Stage IV (85%) disease who achieved a complete remission under a chemotherapy regime called ProMACE were entered into the study. These twenty patients were given four monthly idiotype-KLH injections + GM-CSF followed by a booster shot identical to the previous injections at 6 months. The injections were given at least 6 months after the completion of chemotherapy to allow the immune system time to recover. Of the 20 patients 18 remained in continuous first complete remission at an average 42+ months from completion of chemotherapy. Of these 20 patients 11 had detectable translocations in their tumour cells allowing the cancer to be tested for in their blood. All 11 of these patients remained PCR +ve (lymphoma cells still detectable in their blood) after their chemotherapy, even though they were in complete remission. Upon completion of vaccination 8 of these 11 patients (73%) had become PCR –ve. This is termed a molecular remission and means that lymphoma cells could no longer be detected in the patients blood. The sensitivity of the PCR test employed meant that it could detect 1 malignant cell in 100,000.

When looking at the type of immune response generated 75% of patients developed an antibody response and 95% developed a cytotoxic T cell response.

In a review article written in 2001 by Bendandi one of the co-authors of the 1999 paper it mentions that 39 patients had been enrolled in the above study, of whom 25 achieved a complete remission. Among these 25 patients one relapsed within 6 months and two were not immunized because of technical problems in producing the custom-made vaccine. Following this he states
'yet it is remarkable that with a follow-up ranging from about 3-6 years, 19 of 22 patients maintain their first CR'.

What other journal articles using idiotype vaccines in humans have been published?

Study 2: Tumour-Specific Idiotype Vaccines in the Treatment of Patients With B-Cell Lymphoma-Long-Term Results of a Clinical Trial. Hsu, F et al. Blood 1997.

In this study 41 patients were vaccinated with idiotype-KLH and instead of GM-CSF another adjuvant called SAF-1 was used. Of the patients vaccinated 20 developed an anti-Idiotype (Id) immune response. Of 15 patients who were vaccinated while in remission and made tumour specific immune responses 13 were still in remission 8 ½ years after the cessation of chemotherapy when the paper was published in 1997. From an update in Hematology 2001 it appears 60% of the original 20 who mounted an anti-tumour immune response have maintained their remission and are still disease free at 10+ years. That word cured starts creeping into ones mind. Those not mounting an immune response or vaccinated while not in remission were far more likely to have disease progression.

Although the numbers enrolled in each of these studies were small. When you compare freedom from disease progression and survival curves to historical figures there appears to be a clear benefit to patients treated with immunotherapy in whom an anti-tumour response is elicited. It also appears that the best responses occur when a patient is vaccinated when in complete remission.

The results have been so encouraging there are now two large Phase III trials underway in the US. These are recruiting hundreds of subjects. In one of the studies all patients will be given a chemotherapy treatment CVP. Of those having a complete response two-thirds will be given the Id-KLH+ GM-CSF vaccine, the other one-third will receive a placebo (dud) vaccine. Understandably, although many thousands are diagnosed with Follicular Lymphoma each year in the US, subject numbers have been slow to accrue. Would you want to be given a dud vaccine? I am surprised it got through the ethics committee. When the difference between getting a vaccine and not getting it will most probably mean the difference between life and death for the subject, a placebo arm is frankly a stupid/ inhumane thing to incorporate into the study design. Its not like we don't already know the likely outcome for those given CVP + placebo. For the last few decades we have been watching people come out of remission time and time again after being given CVP. I am sure one could build a freedom from progression and survival curve based on historical data. It seems to me that for the sake of some anal statistician or some corporate interest they want to prove over and above all possible doubt the effectiveness of their vaccine (which could be proved in a number of more ethical ways). For this reason patients are being asked to lay it on the line. A few years ago a similar thing was tried by a pharmaceutical company who were trialing HIV drugs in pregnant women in Africa. They had a placebo arm also in this trial. There was a huge public outcry. A far better study design would have been to compare perhaps two different vaccine strategies eg. idiotype-KLH + GM-CSF or IL-2; perhaps idiotype-KLH+GM-CSF vs idiotype-KLH+ GM-CSF followed by DC vaccination.

Anyway they are the ones who have to sleep at night knowing they have dished out some sugar shots.

The main short-coming of the Idiotype-KLH vaccine is that it takes a long time to manufacture. It can take anywhere from 3-6 months using a hybridoma method. New methods are currently being explored to reduce the production time. Levy et al are looking at generating scFv fragments (basically the variable/ unique region of the antibody molecule) in tobacco plants. Others are looking at instead of manufacturing the actual protein; injecting patients with the DNA encoding their antibody molecule so that cells in their own body can generate the protein. This method has the advantage of taking only 2-3 weeks. Currently only one study in humans has been published and the results were not outstanding but one must keep in mind its only early days and this technique has worked effectively in animal studies.

As far as side effects, these are generally very mild. They are similar to those from a flu vaccine ie. Soreness at the injection site; myalgia (aching muscles); arthralgia (aching joints); mild temperatures. Compared to chemotherapy and radiotherapy the adverse effect profile is minimal.

So lets check out other idiotype vaccine results. For those of you out there who have had stem cell transplants and several lots of chemotherapy and possibly have transformed and feel you are at the end of the road there is this article to bring some hope.

Idiotype Vaccination Following ABMT can Stimulate Specific Anti-Idiotype Immune Responses in Patients with B Cell Lymphoma. Transplantation 2001. Hsu/ Levy et al.

In this study 12 patients with relapsed/ refractory B cell lymphoma who had developed rapid disease progression or transformation were given myeloablative regimens including chemotherapy and total body irradiation. All patients had a Complete Response prior to vaccination.

There were 2 vaccination schedules.
8 patients were given Id-KLH+ SAF adjuvant 5 injections.
4 patients were given 2 idiotype dendritic cell infusions followed by 5 Id-adjuvant vaccinations all given at monthly intervals.

Out of the 8 given soluble protein vaccine 6 out of 8 remain in remission with follow up > 6 years range 3-11 years. Of possible note is that the 2 relapsing patients were vaccinated 2 months following ABMT ? Given a tad too early.

Those given the combination regime including dendritic cell infusions 1 out of the 4 continues without relapse now at 4 years post ABMT. The other 3 patients have relapsed.

Very small population sizes again make it difficult to really draw firm conclusions.

Another article.

Anti-idiotypic Vaccination in the Treatment of Low-Grade Lymphoma. Haematologica 2002. Barrios.

9 patients with Stage IV low grade NHL.
A variety of previous treatments including multiple chemotherapy and ABMT/ ASCT.

5 were vaccinated in CR 4 were vaccinated in PR.
Of interest 2 out of 12 patients enrolled in the study showed bi/triclonal tumours. This means that all of the cancer cells in these two patients did not have the same antibody on their cell surface. One patient had 2 cell populations/ clones with a different antibody molecule on each. The other had three different lymphoma cell clones, each group with a different antibody molecule on its surface.

Now this gets a bit technical. Each B cell has the ability to slightly alter the antibody on its surface. It does this by introducing point mutations in its genetic code which very slightly alter its antibody. In the vast majority of patients with lymphoma the cancer cells all come from the one clone ie. They are monoclonal. But within this monoclonal population there are cells which have undergone somatic hypermutation/ point mutations and the antibody molecule on their surface is slightly different to the original tumour cell. Now a study by Levy has shown that anti-idiotype vaccines generate an immune response which should cover these point mutated cells. As well as attacking the main tumour cell some of the snipers also undergo this slight alteration which allows them to attack the variant cells. The immune system is able to mount a polyclonal immune response to cover the slight shift in some of the tumour B cells. Now the patients in this study did not have cells with a slight shift. They had two or three totally different lymphoma cells of origin. Thus they had to be given 2 or 3 different anti-idiotype vaccines.

Of the 5 patients in CR at the time of vaccination 4 remain in CR at 38 months. Patient 2 relapsed between the 4^{th} and 5^{th} vaccine dose but completed the vaccine course. Their tumoural masses persisted on CT for 6 months before diminishing and disappearing, they remain in CR at 64 months.

Of the 4 patients vaccinated in PR patient 1 died of unrelated causes. Patient 3 had tumour regression for 3 months but relapsed 7 months later. They received oral cyclophosphamide for 10 months and have been in CR for 56 months. The amazing thing is this patients previous treatment included several chemotherapy lines and APSCT so you would expect cyclophosphamide to be next to useless. The other 2 patients haven't had tumour progression since vaccination.

So they are the Soluble Protein Vaccine Results which have been published currently. There is also a study looking at Dendritic Cell Therapy in Follicular Lymphoma. Dendritic Cells are like army drill sergeants. They shout and carry on and try to stir up the troops. When using the Id-KLH injection we are trying to activate these dendritic cells while they are still in the patients body so they will go out and train some snipers to kill cancer cells.

Dendritic cells are basically antigen presenting cells. They absorb debris, work out what has come from your own tissues and what material has come from a foreign source (eg. invading bacteria). They present this foreign material in special receptors on their cell surface to the immune system. This triggers the formation of sniper cells. These may be either B-cells which convert to antibody factory plasma cells or T-cells which are cell to cell killers.

The vaccines mentioned previously recruit dendritic cells in a patients body by attracting them to the area with chemical messengers such as GM-CSF or IL-2. Dendritic cell therapy takes dendritic cells out of the patients blood manipulates them in a test tube and re-injects them. The process of separating dendritic cells from a patients blood involves leukophoresis and density gradient centrifugation. This in some ways takes the guess work out of vaccine manufacture. You have the dendritic cells in a test tube and can basically have your way with them, controlling what they are exposed to at what stage of development. Once the dendritic cells have been re-infused into the patient, the patient is given injections of their idiotype protein.

Idiotype Pulsed Dendritic Cell Vaccination for B Cell Lymphoma: Clinical and Immune Responses in 35 patients. Blood 2002. Timmerman/ Hsu/ Levy. Man that Levy has published a heap of papers. He must be going for a Nobel Prize as patients we can be glad he has an interest in B Cell malignancies.

Obviously from the title 35 patients were involved.
10 patients had measurable disease with no recent treatment.
25 were vaccinated after an attempt to put them into 1st CR.

Patients were given antigen pulsed DC infusions monthly for 3 months. A 4th booster infusion was given 2-6 months after the 3rd.

Results:

Patients with Measurable disease and No prior cytoreduction.
1 Molecular Disease and post vaccine has had no evidence of disease for 79+ months.
2 Complete Remission duration 44 and 57 months with disease recurrence.
7 Disease Progression median 8 months following DC vaccine.

Patients Attempted 1st CR prior to Vaccination:
5 Vaccinated while in CR- 4 patients no evidence disease 40 months 1 progressed at 21 months.
20 Vaccinated with disease present:
4 patients regressed to no evidence of disease; 1 regression to Minimal Residual Disease 46 months.
7 patients stable disease: Median 36 months.
8 patients progressive disease occuring on average 19 months post vaccination. Range 9-28 months.

70% Remain Progression free at Median 43 months post chemo.

Another portion of the study involved giving patients with persistent/ relapsed tumours after DC vaccination soluble protein booster vaccinations. Of the 6 patients treated.
1 CR 48+ months.
1 PR 14 months.
1 Cru (unconfirmed Complete Response) 16 months.
3 Progressive Disease.

In those failing dendritic cell therapy 3 of 6 patients had a clinical response to soluble protein vaccine.

As you may have gathered the two principle sniper cells in the immune army are B cells and T cells. As previously mentioned B cells are antibody factories. You may hear the term humoral immunity, this refers to the B cell antibody arm of the defence system. B cells could be likened to a meat works, they pump out steaks which coat the target cell resulting in the non-specific immune system, the guard dog, mauling it to death. T cells are the blind boxers who are involved in cell mediated immunity. They move along feeling each cell they pass and when detecting the specific cell they're primed to, deliver it a knock-out blow. It appears that soluble protein vaccines such as Id-KLH+ GM-CSF mainly trigger off a humoral or B cell immune response while DC therapy mainly triggers off a T cell immune response. Of course if both arms of the immune defence can be engaged at the same time it is likely that a greater anti-tumour response can be elicited.

Summary.

Ones treatment choice when diagnosed with Follicular Lymphoma is ones own. You should if you are so inclined seek out accurate information/ advice and make the best decision for your particular circumstances. I am 28 years of age and so my treatment decisions may be totally different than those of a person diagnosed at 65.

For a young person I feel the emphasis should be on curative treatment. We don't really want to live 18 years instead of 10, we would like to have a shot at eradicating the cancer. When looking at potentially curative treatments there really isn't enough data out there to know you are making the best decision. It is a gamble, you look at the form guide and try to pick a winner.

For myself if given any treatment to choose from I would pick in order of preference:

1. CVP with CR followed by Id-KLH+GM-CSF (not dud placebo) inducing a molecular remission. This regime should be minimally toxic and hopefully result in a cure.
2. CHOP+Mabthera
3. If these options are not available due to government restrictions on access then I would give it a shot with currently available treatment. An Anthracycline chemotherapy regime with adjuvant radiotherapy. If available down the track a vaccine would probably boost the cure rate even more.

If these failed to induce CR then there is a difficult decision to make. Do you press on with more and more toxic therapies to get to CR before a vaccine or do you give the vaccine a go even if you are in PR (that is if you have access to a vaccine). Well this is difficult. Again no-one knows the future and what break throughs may be just around the corner. As we have seen vaccines in PR can halt disease progression in a majority of patients for several years and counting. You could have the vaccine to halt the disease in the hope that over the next few years a very successful treatment comes along. Alternatively you could hit the remaining tumour hard and with minimal disease present try to get access to a vaccine. We have already seen that durable remissions are possible in heavily pretreated patients who receive a vaccine following ABMT.

Now this approach could burn through several bridges in one foul swoop. That is the risk you take. If you were an elderly person 60+ on average you can expect 8-10 years with current treatment. You may be happier to burn your bridges one at a time and avoid toxic therapies. Thus you may start out with a mild chemotherapy regime then once that fails move on to Mabthera etc. Mind you some people at 60 may well have another 40 years to go and opt for a more aggressive plan.

Anyway I'm not your doctor. I hope the information has enabled you to have a better understanding of the options available. Although specialists are knowledgable they often have their own treatment prejudices and can present a very lopsided view at times.

One thing I would like to see happen is for a group of patients to grab hold of their own destiny and fund the building/ staffing of their own vaccine factory. Currently academics are firmly in control of how many vaccines are offered, who can get them etc. Why let others dictate to us whether we will live or die. There is an effective treatment with a minimal toxicity profile, there must be haematologists/ molecular biologists etc who would like to assist/ oversee such a project. If there were a vaccine for HIV with 10 years follow-up data would you have its access to patients being so heavily restricted. It really isn't that difficult to generate scFv from a patients tumour sample. There are a wide range of commercially available transfecting kits at minimal cost. Lets give the plodding academics some competition. There are 50,000 people diagnosed with NHL in the states each year. If everyone newly diagnosed person donated $10/ week that's $500,000/ week. You could run a decent sized lab there for that amount of money and start generating some decent trials. If you are waiting for the government to come to the rescue or the researchers to satisfy themselves that everything is perfected you will probably be waiting a very long time. I will be surprised if the vaccine is available within 5 years; more likely 10 it will take that long for those in the current trial who are going to pass away to expire so some useful statistician can have attractive graphs.

Anyway I pray the decisions you make with regard to treatment are the best ones possible and that whatever road lies ahead for you it brings you closer to the truth and the things that matter.

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