First Waldenstroms Research Work Group Meeting

September 8, 2000
Bethesda, Maryland

AM Session:

1. Classification of Lymphoplasmacytoid Disorders and Practical Issues in Multi-center Clinical Investigations [Sandra Horning]

   Group discussed a formal definition of WM, however, they did not come to agreement.

   Comments by participants were:

   a. Have to define it so that patients aren't over-treated or under-treated.
   b. People who are borderline need to be diagnosed with one disease or another.
   c. Virus-related from Hepatitis C, or Barr-Stein ?
   d. Auto-immune connections?

2. Familial Waldenstrom's Macroglobulinemia [Mary McMaster]

   a. No evidence yet of genetic transmission, but relatives may have high IgM without WM.
   b. Still looking at survey results but not enough participants yet. There are some family members with WM, but it is possibly under-reported. Of fifty families reporting, one-third have two or more immediate relatives with WM.

3. Staging and Prognosis [Morel, Rohatiner, Fonseca, Dhadapkar]

   a. France uses: Hemoglobin less than 12, and albumin levels for diagnoses. See BLOOD Journal, August 2000 for Dr. Pierre Morel's scoring system.
   b. England: Worked with Sweden, and uses IgM over 2,000. Overall survival - hemoglobin and albumin mattered. Age didn't.
   c. In Sweden many were untreated, and in England most were treated. Sweden had much better survival rates, but believes it's from referrals coming in at different stages in the disease.
   d. Mayo sees 150 cases a year with high IgM, but treat only a fraction. They see a lot of what they are calling "smoldering Waldenstrom's."
   e. In England and France, all had defined WM as Bone Marrow infiltration.

f. Mayo: (Fonseca)Lymphoplasmacytoid cases are only 5% of NHL cases. They have looked at translocations(9-14, p13-q32) but couldn't find any case with these translocations. The reviewed 20 patients BM slides, stained for IgM producing cells and found no translocations, no deletions.

g. NYC/Rockefeller: (Dhodapkar) Was formerly at U. of Arkansas with Barlogie and SWOG. Studied impact of therapy on survival. Used variables of IgM, B2M and others. But high hemoglobin and low IgM in untreated WM were important factors to survival. IgM and B2M counts in treated patients were significant to their survival. With low IgM, no treatment is needed. However, those with high IgM do badly without treatment. High Hemoglobin (over 12) and low IgM in the untreated is being called "smoldering WM" and has high survival rates. There's a big difference in the treated and untreated patients. He looked at using risk-based approach to management of WM for treated and untreaded. Used purine analog and alkalating agent as standard therapies for WM.

4. Current Therapies [LeBlond]

a. Dr. LeBlond (France) had studied Fludarabine compared with Chlorambusil. The survival rates were similar, however, those using Fludarabine did better.

b. Donna Weber spoke about not treating those with less than 10% BM involvement, with under 3000 IgM, and with no symptoms. She mentioned 2CdA as being the same treatment as for Hairy Cell Leukemia, and said that nucleoside analogues were not good for about 18% and they shouldn't take them. The see improvement in about 75%, but the DNA damaging effects are a problem. Tried combining 2CdA with cyclophospamide, but response was not better, although it was better overall than responses to CHOP. With Rituximab the results were much better. With Rituximab plus 2CdA and Cyclophospamide it was even better.

c. For the WM asymptomatic patients it was suggested they stay on Watch and Wait, or use Thalidomide possibly, although they are seeing a lot of neuropathy issues from Thalidomide. Also, perhaps Interferon would be better for asymptomatics. It will take some time to analyze this.

d. Mayo (Rajkamur) You must be careful of going after Complete Remissions. Those who are doing well after treatment, if you treat again later on and they still do well, this only means they are good responders. Must be careful to not ad more and more therapies to those patients. It's not good.

Question: What should standard therapy be?
Comments/Discussion:

- With erythropoetin, can help anemia so they don't need further treatment.
- Group that increased from 11 to 12 hemoglobin had the maximum increase in quality of life. There are quality of life issues here.
- Erythropoetin is used for low hemoglobin (-10) and with symptoms. Anemia drives it all. He doesn't want to see standard treatment, but we have to define when to start treatment.
- At what level is treatment need?
  - 5 x anemia
  - 8 x adenopathy/organomany
  - Lymphnopathy
  - Neuropathy [using plasmapheresis]
- Watch & Wait doesn't mean ignoring the disease. Must be constantly monitored to know when to treat without waiting too long.
- Looking for anemia, fatigue, cytopenia less than 1.5, splenagamy, platelets less than 100,000, and hyperviscosity. Not well-defined as to when to intervene. Must be monitored very closely, and it's also a matter of judgement and experience with the disease.
- There is still a six year median survival. Two years is a lot, if treatment gives you two more years.
- Follicular lymphomas have the same problem – deciding when to treat. With WM you have a marker that other diseases don't have - IgM. IgM can remain stable as IgG rises. Gertz always measures IgM, total protein and IgG. IgM and IgG go together. The M spike is measuring bad IgM, not good IgM.
- Treating with What? Age is an issue. Older patients don't respond as well. Maybe with older patients you want to focus on protecting quality of life instead of high level treatments for a CR that you might do with a younger person.
- If there is a rapid rise in Creatine, need therapy immediately to move it down.
- So with alkalating agents vs. purine, it's an issue of how much and when. In absence of data, it's tricky and there's the issue of toxicity.
- Frankel: We must take a look at these three - Thalidomide, Interferon, and Rituxan. They are available and they are being used. Need to consider what goes onto PDQ (the NCI website). Currently PDQ says Rituxan may be considered for those for whom other therapies didn't work !
- It's difficult to write a guidance for treatment when there's no agreement.

LUNCH BREAK----------

PM Session

5. New Strategies

a. Al Katib is working with SCID mice slides and sees light chain switching. They saw this in their cell lines.

b. Bruce Cheson mentioned new chemo agents for NHL they are testing and may have some news in the future:

Mechanism	Agent
Cytolovic	Oxaliplatin
Apoptosis induction	Retinoids, arsenicals
PKC inhibition	Bryostatin
Cycliln inhibition	Flavopiridol
Farnesyl transferase inhib.	–
Histone deacetylation	Depsipeptide
Antiangiogenesis	Thalidomide

c. Rajkuman: Antiangiogenesis agents for WM and MM - Thalidomide used in MM, and he suggests use with WM. Recommended anti VEGF therapies.

d. NCI wants LOIs for 5416 trials with WM Phase I. They just finished the solicitation. Thalidomide trial proposals were not received for WM. NCI is also soliciting for Phase II trials.

e. Treon: Novel targets - Rituximab for WM - 30 patients, 90% express CD-20, all needed treatment. Rituximab cleans out blood, not so good on organs. Hematocrit - 60% increased, platelets increased.

f. Data gathered from many institutions who have administered Rituxan to WM patients: PR: 27% (8); Minor response: 33% (10); Stable disease: 30% n= 27 patients.

g. Grippe: ECOG Myeloma Committee interested in WM. Joined SWOG study. Had 72 patients in two years. Interested in new regiments, doing Rituxan Phase II design. Impressed by accrual. Most entered last three months. Could finish in 1-2 years with SWOG joining ECOG.

h. Gertz: ECOG proposal for trials: 1) simply eligibility, ease of administration, 2) simple for community implementation, 3) studies for every phase of disease, 4) survival not primary end point – WM patients live longer.

i. Kyle: Studied 46 patients on Chlorambucil: Response in 88%; Survival: 65 Months; 10% developed myelo-displacia symptoms from chlorambucil. 2CdA - 100% response in the untreated patients. Toxicity = infections. Slow platelet recovery.

j. Chlorambucil, Rituxan, Fludarabine, Cladribine, Thalidomide, all are active. We don't know the best regimen.

Group tried to define WM patients who are untreated and shouldn't be, in order to protect patients who need only to be observed (Watch and Wait).

Some proposed trial designs:

1. Randomized Phase II: Untreated: Rituxan first to reduce cytopenias, then one month's rest; 2CdA (6 weeks x 3); Chlorambucil (1 year). Don't need to be a Rituxan responder. Treated: Thalidomide (1 year), anti CD20 single dose Levalin.
2. Interested in CD 20 - Previously treated, in plateau phase, IgM over 1000, BM involvement, CD5-, CD23-, less than 25% lymphocytes. Could you kick-start into a lower level of the disease?
3. Relapsing or Refractory Disease : Thalidomide. Or Zevalin. Can take Zevalin after Rituxan.

CLOSING:

The group will need to have a follow up meeting. Still no closure on many issues for WM patients.

NOTE: These notes were provided by IWMF observers