January 2018

Northside Multiple Myeloma Support Group Meeting
January 6, 2018

Northside Meeting – ASH Review at Emory

Over 60 people attended the ASH review at Winship. Many thanks to the Winship team for providing the full breakfast to the attendees. Also, thanks to Takeda for the pizza at lunch.

The first to speak was Dr. Nooka. He noted that he has been at Emory for ten years. He has seen survival rates improve over that period. Great outcomes are being seen in the induction therapy of RVd (Revlimid, Velcade, dex). Studies have proven that three drugs are better than two drugs and the triplet is achieving 100% response rates after four cycles of treatment. Transplant after induction therapy is deepening response rates and leads to longer remission. PFS (Progression Free Survival) charts show 50% do not progress at seven years and OS (Overall Survival) is 75% at ten years. For standard risk patients (no abnormal genetics), the survival is 85% at ten years. Statistics are also showing these rates at Emory are higher than other Myeloma centers, such as Mayo and Arkansas Total Therapy. Further studies are needed for long-term follow-up. Clinical trial GEM2012 used RVd for six cycles, but the results were the same as four cycles at Emory. The extra cycles introduces extra toxicity without delivering improved efficacy, unless the patient is not eligible for transplant, then six cycles would be of value. Velcade, a proteasome inhibitor (PI), has caused peripheral neuropathy, so there are other versions of PI available. Carfilzomib (Kyprolis) is an approved PI, but it has higher toxicity and many patients cannot tolerate it for long periods. Ixazomib (Ninlaro) is an oral PI, but does not get the same response as Velcade. How about a fourth drug or adding a monoclonal antibody? Adding Elotuzumab (Empliciti) as a fourth drug is well tolerated. Ongoing clinical trials are looking at Rd + Daratumumab (Darzalex) for up-front treatment and evaluating results over the long term.
One of the primary questions from patients: Is a transplant still necessary? A trial in Europe is giving patients VCd (Velcade, Cytoxan, dex) to newly diagnosed patients and then splitting them into two groups: transplant vs. four rounds of VMP (Velcade, Melphalan, Prednisone). Then both groups go to consolidation and maintenance. PFS at 36 months is 64% with transplant vs. 57% without and ORR (overall response rate) is 84% with transplant vs. 75% without. Another trial in Europe is looking at double transplant vs. single transplant. Note that the induction therapy is different in Europe (not RVd).

Other trials that Dr. Nooka discussed included Revlimid maintenance showing PFS of 57 months vs. 30 months without maintenance for both transplant eligible and ineligible patients. The FDA approved

Revlimid for maintenance in February 2017 after trials showed a 50% overall survival (OS) at 10 years with maintenance vs. 50% OS at 7.5 years without maintenance. Another question being addressed: Should patients get maintenance if they achieve Complete Remission (CR) after transplant? Trials are showing better OS with maintenance and the same benefit for high-risk patients.
Studies on long-term Ixazomib (Ninlaro) show a 3-4% risk of secondary cancer, about the same as Revlimid. The risk of Myeloma is significantly higher without maintenance vs. secondary cancer. Ixazomib (Ninlaro) is a good alternative to Revlimid and is also a convenient oral medication. This is from several studies on maintenance where the average PFS is 33.6 months. More studies are underway and Dr. Kaufman is leading a trail for Revlimid vs. Ninlaro maintenance. There is also a trial comparing ERd (Elotuzumab, Revlimid, dex) vs. Rd as maintenance. Preliminary results show VGPR 74% with Rd vs. 91% with ERd. With all the combination choices, in Emory's opinion for maintenance, it is better to use as few drugs as possible because of the side effects and not all patients should be on a combination of drugs. Results improve with maintenance after consolidation, but evaluation of each patient is needed to determine risk of relapse.

MRD (minimal residual disease) is the hot topic these days. This is the testing of the bone marrow to find the myeloma cells when a patient is in remission. The more sensitive the test, the better the outcome. There are two tests: NGF (next generation flow) and NGS (next generation sequencing). The flow test with eight colors is looking for one myeloma cell out of 100,000 marrow cells, 10^{-5}. Doing the more sensitive flow test with ten colors can find one myeloma cell in one million marrow cells, 10^{-6}. If the more sensitive test comes up negative, considered MRD-negative, then trials show that 90% of those patients hold complete remission much longer. MRD-negative is also showing longer survival rates, but more studies are needed before these tests can influence treatment protocols or breaks from treatment.

Dr. Nooka took questions before he had to return to the hospital.

Q – Why is MRD not a routine test on all patients in remission? **A –** Insurance does not cover the test and can cost up to $1500. Last year, the flow test was free as the labs were getting certified and collecting data on patients. Now it requires pre-authorization from insurance and may not have immediate prognosis value. Dr. Lonial stepped up to address MRD. He said that there is lots of hype on the clinical value, but MRD doesn't impact treatment decisions at this time. They are still collecting information to see what it really means across a large data set. Most MRD data available now is from Europe, but they have different treatment protocols where many of the novel agents are not available outside of clinical trials.

Q – When? A – Studies are being designed now and it will take 3-5 years for the study results to be collected and evaluated.

Dr. Craig Hofmeister will be joining the Winship team, effective February 1, as a physician and researcher. He is coming from Ohio State University in Columbus, OH. He was available to be at this ASH meeting and was the next speaker. Dr. Hofmeister talked about daratumumab, a monoclonal antibody that attaches to CD38 on the surface of myeloma cells and some other cells. Daratumumab (aka Dara) also invigorates the immune system to cause myeloma cell death. Dara works as a single agent, showing results in one out of three relapsed myeloma patients, or 33%. When Dara is combined with Revlimid and dex, it works in nine out of ten cases (90%), where Revlimid and dex works in seven out of ten relapsed cases (70%). Tests are underway to inject Dara subcutaneously (sub-Q). Dara through IV take up to 12 hours for the first dose and later infusions take 3.5 hours. The sub-Q can take only 3-5 minutes. Dara is injected with an enzyme to allow the drug to get into the skin and not hurt. The injection site can get hard due to the volume of liquid. The sub-Q injection of Dara shows more active drug in the patient system and less side effects. Sub-Q patients had 12% side effects vs. 60% with the infusion delivery method. More studies are needed.

Dr. Hofmeister talked about smoldering Multiple Myeloma (SMM) and the new Mayo clinic criteria for progression to active MM. There are three criteria that determine progression. When the patient has zero, one, or two or more of the factors then the study showed percentage chance of progression within five years. Criteria are M-protein $\geq$ 2 g/dL; $\geq$ 20% clonal bone marrow plasma cells; and Free light-chain ration > 20. If none of these criteria, then there is a 23% chance of progression in five years. If one of these criteria, then 47% chance of progression in five years. If two or more of these factors, then an 82% chance of progression. A lot attention is focused on SMM lately and how to determine when treatment is needed to avoid damage from active MM.

A study of high-dose flu vaccines in MM patients was discussed by Dr. Hofmeister. Myeloma patients are 6-fold higher risk of influenza. A trial at Mass General tested high dose flu shot, repeated 30 days later, and compared it to one standard of care flu shot. One dose of standard flu shot had 45% protection at one month and 30% at two months. After a second dose of flu shot, there was 52% protection. Who needs more intense vaccination strategy? Myeloma patients on active treatment (not maintenance), patients age 65 or older, or patients with poorly controlled myeloma need more flu protection.

Dr. Hofmeister reviewed a report in the UK that found infection is the primary cause of death in >20% of myeloma patients. Data in leukemia patients showed that prevention with antibiotics was beneficial. A study was created to give Levaquin 500 mg daily to newly diagnosed MM patients for three months. Deaths from infections or myeloma within three months of starting myeloma treatment were reduced by more than 50%. There were also fewer hospital admissions due to infections and less use of antibiotics for these patients. Dr. Hofmeister's last comment was that he loves acyclovir. It is cheap and has few side

effects. Shingles occurs in only 0.5% of myeloma patients actually taking any dose of acyclovir.

Dr. Kaufman talked about new treatments and new combinations. Clinical trial GSK2857916 was testing an antibody drug conjugate as a single agent. An antibody drug conjugate is using the unique targeting capabilities of monoclonal antibodies combined with the cancer-killing ability of cytotoxic drugs. Antibody drug conjugates allow the monoclonal antibody to bind with the BCMA on the myeloma cell and deliver the chemo only to those cells with BCMA. Of the 35 patients on this study, over 90% were refractory (had disease progression during treatment) to both Revlimid and Velcade. This treatment resulted in an overall response rate (ORR) of 60% in heavily pre-treated patients and 51% had VGPR (very good partial response) or better. The drug was well tolerated and side effects were manageable. The study is ongoing and future studies will include combinations. This trial may be available at Emory. The mechanism of this therapy is different from currently approved drugs in MM, which is exciting news. Dr. Kaufman also talked about studies including Dara with Velcade, melphalan and prednisone (D-VMP) vs. Velcade with melphalan and prednisone (VMP) for newly diagnosed patients, age 65 or older and ineligible for transplant. This study was in Europe to show the difference in adding Dara for new patients. The ORR was 91% for D-VMP vs. 74% for VMP. At 18 months, 72% of the D-VMP patients were progression free, while 50% of VMP patients were progression free. The D-VMP group also had a MRD-negative rate at three times higher. Dara is also being used in amyloidosis. Dr. Kaufman also talked about Venetoclax that works differently than other MM drugs. Apoptosis is a regulated and controlled process of cell death within a specified lifecycle. BCL-2 overexpression allows cancer cells to evade apoptosis. Venetoclax binds to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death. The ORR in this study was 21%, but it was 40% for t(11:14) high risk MM patients and only 6% for non-t(11:14) patients. Adding dex improved the high-risk response from 40% to 65%. This drug will be moving to a larger study on t(11:14) patients.

Dr. Lonial presented Immune and CAR T Therapies. He talked about three types of immunotherapy. Passive Immunity is the monoclonal antibodies that target a receptor on the surface of the myeloma cell, a truly targeted therapy. Adjuvant therapy is add-on therapy such as a peptide vaccine or dendritic cells that are messengers between immune systems. These treatments are not generally effective. Active therapy involves delivering cells to the immune system through allo transplant or CAR T-cells. Dr. Lonial cited four different CAR-T therapies that are available in clinical trials. This is a hot topic, but which strategy and what timing for patients are difficult questions. CAR-T therapies are not all the same. The difference between the different therapies is not known until there is more data. The challenge with CAR-T procedures is that it takes 28 days after harvesting to make the T-cells. Patients need to be well enough to wait for the cells without the myeloma advancing to a critical level. Responses are very good, but toxicity is not minimal and requires a specialized center for delivery. Cost ($500,000)

and payer considerations are also an issue. Manufacturing of T-cells and capacity are a limitation. Emory will have five different CAR-T opportunities for patients in the coming months.

Dr. Lonial announced the Myeloma doctors joining the Team at Winship in the next few months. Questions and discussion followed.

Q – Should a myeloma patient get a second flu shot? **A –** The standard practice has not changed, but a second shot would not cause harm. It also depends on how effective the vaccine is against the current strain of flu. **Q –** What are the side effects of Levaquin? **A –** Need to be careful since it has been overused in the past. Monitor the impact on the kidneys. The UK uses a cytotoxic treatment which could justify the Levaquin. **Q –** The number of patients who are getting transplants are lower than the ones who qualify for transplant. Why? **A –**Patients who could benefit from a transplant are not getting them. The gatekeeper is the community oncologist. Emory educates the community doctors and the support groups can inform patients and have them ask about transplants. **Q –** Any reason not to take Acyclovir. **A –** Prior exposure or a reaction. Very uncommon to have any problems. **Q –** Even with Acyclovir, there is a 0.5% risk of getting shingles. If a patient gets the shingles while on Acyclovir, will it be a mild case? **A –**Yes, possibly. **Q –** Likely to get shingles in the same location? **A –** We don't know. You could feel pain and symptoms with a virus. **Q –** There are many relapse combinations, such as Ninlaro/dex, Dara/dex, etc. What are the latest combinations? **A –** Pom/Dara/dex is being used in trials, but not approved. The new combinations show benefits early. **Q –** Can patients from other clinics participate in clinical trials at Emory? **A –** A referral is needed. All MM trials are done on the Clifton Road campus. **Q –** Using MRD, is there a way to predict tumor growth rates? **A –** The goal of predicting disease trend is a question from all doctors. More data is needed. They may use the current date, but that is not enough. **Q –** When will there be an MRD test on blood vs. bone marrow? **A –** Blood tests are much less sensitive for now. **Q –** Is there a correlation of Revlimid dose level on progression free survival? **A –** We are not sure, but don't think that there is impact from higher doses. **Q –** What is the CRISPR therapy? **A –** This is gene editing and it is generating big news in blood disorders. It may apply to myeloma, but only one trial at Penn and it is not open. A trial may come to Emory later. **Q --** Should MRD testing be done when newly diagnosed? What testing intervals? **A –** MRD should be tested at remission. Emory tests at one year after transplant and annually thereafter. **Q –** Do you see any changes to maintenance therapy? **A --** Ninlaro may fit in, but they do not have a large set of data to support it. Doctors know how well Revlimid works and have the data to show results. Need to see what happens with Ninlaro. There are trials adding monoclonal antibodies (Dara and Elo) to maintenance. **Q –** With the continuing rise in cost of MM treatment, how will cost impact future therapy, especially with CAR-T costing $500,000? **A –** We do not discuss cost, just toxicity. Financial toxicity will have to be addressed. Dr. Lonial said that their approach is to cure or achieve long-term PFS. They are pushing the envelope of therapy and focus on patient outcome. The five year plan is to increase cure rate and WIN! A

cure can justify the cost. **Q –** If CAR-T provides a cure, then would the insurance companies recognize that the one-time expense is justified to avoid the long-term high cost of maintenance? **A –**Good point, but not seen by the outcomes. **Q –** When will Data be available sub-Q? **A –** It is in a trail at Emory and we predict approval in 2.5 to 3 years. Just finished Phase I six months ago. It is in Phase III trials for amyloidosis.

Notes by Nancy

Southside Multiple Myeloma Support Group Meeting
Saturday, January 27, 2018

There were 22 present, with one new member.

March meeting: Speaker: Jennifer Rooke, MD, MPH, The Role of Plant-based diet in prevention and control of disease.

We welcomed a new member, Mrs. Emma S. who attended the meeting with her husband, Turner, and two sisters, Mary K. and Mildred K. Emma was diagnosed on December 24, 2017. She had gone to the ER in Fayetteville twice with severe pain. After a CT scan, she was diagnosed with bone fractures. She is being treated by Georgia Cancer Specialists and Northside Hospital. So far, she has had two weeks of treatment with Revlimid, Velcade, and Dex (RVD). For pain, she takes morphine/oxycodone. On February 13, she will have a consultation with the Myeloma specialists at Emory Winship in the next few weeks. Emma is originally from near Albany, GA and became reacquainted with another patient she knew from High School in their hometown.

Updates
Those who attended the ASH Conference update on January 6 at Emory, were asked, "What were some of the highlights for you from the presentations from the Emory Myeloma specialty team -- Drs. Nooka, Kauffman, Hofmeister, and Lonial? Larry was impressed with the new technology and some of the progress of some clinical trials; he was excited about the increase in life expectancy and precision/personalized medicine reports that includes genomics studies; Carole was impressed with the entire experience of having physician researchers share national and international advances – of course, sometimes the information was overload. The number and resumes of new myeloma doctors was impressive, including Dr. Hofmeister and his sense of humor –also naturally excited about the increase in life expectancy; Jameca was also impressed by the growth of the staff, research and MM patient load at Emory (from about 100 MM patients in 2000 to more than 1,600 in 2016. Dr. Lonial and his passion is impressive – and reports on working to lessen side effects as new drugs are introduced; Vermell was impressed by all the others reported, and additionally, the evaluation of the Minimal Residual Disease (MRD); Doris expressed interest in the newer drugs, and on reports of whether the Stem Cell Transplant (SCT) is the optimal treatment. We have heard reports that in maybe 10 years, SCT will no longer be the preferred treatment. For now, research shows that it is one of the best tools available to control MM. Gail

agreed with all preceding comments and added that the growth in staff (2 husband and wife teams, and 2 additional physician researchers) over the past 10 years. Is there an increase in the number of patients with MM – or are we better at diagnosis and treatment so there are more survivors? What more can we do as a Support Group to ensure that we get the message especially to African Americans, so there is not needless suffering? Blacks have 2-3 times more MM than whites. The rate at which blacks get SCT and other quality of life saving procedures should improve. The rate at which blacks participate in clinical trials should improve, especially as we note the effectiveness of more personalized medicine.

We talked about the cost of cancer drug therapy, noting that this could well be a problem with participation rates in treatment and in clinical trials. Each MM doctor should have a Social Worker to help patients who need to find ways to reduce drug costs. Doris brought a 4-page document of financial resources from her last visit to her oncologist. Celgene and other pharma companies have patient assistance programs. Also, for cost of all medications, shop around and compare prices. Some drugs are cheaper at Kroger and Publix. Compare costs of all medications, including high blood pressure and diabetes at GoodRx, as well (https://www.goodrx.com/).

Our speaker was Aaron Streufert, MSN, FNP-BC, a Clinical Nurse Consultant with Celgene Pharmaceuticals. Thank you to Aaron and Celgene for the lunch Aaron brought for the group. Aaron has been a nurse for 10 years – in critical care, as a Family Nurse Practitioner (FNP), and more recently in the BMT (Bone Marrow Transplant) area. He works with Celgene as Nurse Educator and remains on the staff at UAB. He decided to listen to the comments and concerns of those present and to base his presentation on those. He underscored several areas: emphasize quality of life over quantity of Life; know/learn as much as you can about your condition and resources. He gave high praise to the Support Group on their level of knowledge and engagement in their treatment process; control what you can, and do not worry about the rest; there is power in positive thinking; and, you are the most important person in the exam room.

In the 1980s, survival expectation for MM was about 11 months. Currently, 10-15 years is common, and the research for a cure is strong, as reported earlier. He reviewed the CRAB criteria – diagnostic criteria that could indicate myeloma (excess Calcium in blood or urine, Renal problems, unexplained Anemia, and Bone problems).

Aaron described a Stringent Complete Remission (sCR). This means the immunofixation (IFE) is negative (you may follow values on your lab report). It means there is a negative M-spike (or Paraprotein) and that there is a normal Free Light Chain ratio. Status should be confirmed with bone marrow biopsy. Dr. Lonial stressed at the ASH update while the research for testing for Minimal Residual Disease (MRD) is exciting, it comes at an uninsured cost (about $1,500). It should not be at the center of our concerns because treatment or maintenance therapy would likely not change, for now.

The standard of care (showing the best results over time) is the Autologous Stem Cell Transplant (ASCT) – as opposed to the allogenic stem cell transplant (where there is a matched donor for the stem cells). Because the term transplant is so confusing, and is an inaccurate description of the process, SCTs will be referred to as “Stem Cell Rescue.”

Aaron walked the Group through the first 14 days of an ASCT. After the high dose of a potent drug called melphalan, your white blood cell count goes down to zero. The next day, thawed cells are given and find their way into the bone mostly at the breast and hip. The procedure is more like a blood transfusion. With immune system completely gone, patients must look out for possible infections. Though the procedure is simple, it is very dangerous and can cause death. For those who wish to know more about the SCT, you can find information at www.myeloma.org or www.mmrf.org.

Handwashing reminders. Number one cause of death in MM is infection. We are in the midst of one of the worse flu seasons in about 8 years.

Palliative Care is Supportive Care. You may have to ask for these services because they are relatively new in many settings, and providers do not refer to them readily. For people experiencing pain or other health issues that you have not been able to resolve, palliative care may be for you. Palliative care teams are in place to make healing easier for you. It is not related to Hospice, as some people think.

Aaron emphasized that we must remember our Caregivers always. They work extremely hard to try to meet the needs of the patient. With caregivers, patients are reminded that much of healing care includes good nutrition and regular exercise. The Caregiver must also provide tough love for patients. For example, if they see the patient wanting to stay in bed too much, they should take the sheets off the bed!

Jameca has volunteered to be our "keeper of the website" and to review and update the website at least every three months with the help of IMF. She welcomes other volunteers for this task.

Resources/Upcoming Meetings, etc.

· IMF has a new tip card, with the early warning signs of Myeloma. The cards can be ordered or downloaded for free. This is a 2-sided card with a definition of MM. It states that in "70% of patients, the most common symptoms are back or bone pain, fatigue, and recurrent or persistent infections." There is much more information in a simple format to help educate others about MM. We will order cards for distribution during MM awareness month.

· Doris shared a new list of financial resources that she received from her Social Worker at Emory Winship. This is a 4-page document which all of us – patients and caregivers alike -- should review to help relieve some of the financial burden associated with cancer care.

· Ask Dr. Durie. "What is MRD - Minimal Residual Disease?" and "Should a patient take supplements such as selenium?"

· FDA - has expanded the use of Amgen's Xgeva® (denosumab) to include the prevention of skeletal-related events in patients with multiple myeloma. This drug may be an alternative to Zometa or Aredia. It has shown less negative effect on the kidneys.

Some Helpful Vocabulary from this Week's Meeting

Medical Definition of Induction therapy. The first in a series of therapeutic measures taken to treat a disease, typically a cancer. The induction therapy, for example, in myeloma is the initial chemotherapy designed to bring about a remission.

Consolidation is treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells.
(Definition of consolidation therapy - NCI Dictionary of Cancer Terms ...
https://www.cancer.gov/publications/dictionaries/cancer.../def/consolidation-therapy)

What is consolidation in chemo?
The treatment of myeloma is divided into two phases: induction and consolidation/maintenance. Remission induction chemotherapy is administered to produce a complete remission in the bone marrow.

For a more thorough list of terms in myeloma therapy, please see the IMF publication: Myeloma Terms and Definitions: https://www.myeloma.org/sites/default/files/images/publications/tools/glossary.pdf

Respectfully Submitted by Gail

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Please Note: Meeting notes are anecdotal only and not intended to replace advice from your doctor. Feel free to review the discussion topics with your healthcare team.