

Future Directions in the Treatment of Multiple Myeloma Part II

Future therapies may be focused upon treating the microenvironment rather than just the tumor. Take, for example, this 27-year-old gentleman. He had a severe electrical injury in the lower leg (tibia) on both sides. When I saw him 12 years later he had developed lesions in both of his tibia that on biopsy showed monoclonal *kappa* plasma cells (bilateral tibial plasmacytomas). Clearly the microenvironment had changed in the tibia as a result of the electrical injury and the myeloma grew there. We did radiation therapy to the area and the disease has not recurred anywhere during 13 years of follow up. Quite clearly the myeloma could only grow in that environment. This suggests that microenvironmental changes may not only support myeloma growth and spread but in some instances may be required for it.

There are lots of therapeutic targets in the microenvironment of the myeloma cell. IL-6 (interleukin-6) is produced widely by cells of the microenvironment and it is the main growth factor for multiple myeloma. IL-6 signals through a variety of pathways to increase myeloma cell growth, and it may be possible to interrupt these pathways. For example, myeloma cells have adhesion markers which help them stick (adhere) to appropriate cells that they want to stimulate to release the growth factor (IL-6). It appears that myeloma cells must contact the environment to release IL-6.

There are also important elements called VLA-4 and VLA-5¹ that bind to fibronectin² receptors and inhibit the effects of chemotherapy. Maybe in the future we'll be able to combine chemotherapy with ways of affecting the microenvironment to increase the impact on the myeloma cells.

Another critical element is interleukin 1 beta (IL-1 β). It has been shown at the Mayo Clinic that a critical difference between myeloma and MGUS and smoldering myeloma is the expression of IL-1 β by the myeloma cells. Greater than 95% of myeloma patients but less than 25% of MGUS patients are positive for IL-1 β production. It is probably the main agent that stimulates the microenvironment to release the IL-6 back to the myeloma cells. There are inhibitors to IL-1 β called *IL-1 β receptor antagonists*. At the Mayo Clinic, we're testing one of these receptor antagonists called *anakinra* for patients with smoldering myeloma. Anakinra is currently used as an anti-inflammatory for patients with rheumatoid arthritis. Results are still early but it's interesting to see how fairly simple agents which are not chemotherapeutic may be able to attack the myeloma.

The other main route of supply of myeloma growth is angiogenesis³ in the bone marrow. You can progress from low grade angiogenesis where there are a few

¹ Very Late antigen-4 and -5 are adhesion molecules.

² Fibronectin is a protein that interacts with many substances outside of the cell, such as collagen, fibrin and heparin as well as specific membrane receptors on other cells.

³ Angiogenesis is the development of new blood vessels.

blood vessels to high grade, where there are many. Angiogenesis increases in myeloma but not in MGUS and is highly correlated with the PCLI (Plasma Cell Labeling Index) or growth rate. Angiogenesis may be a bystander effect reflecting proliferation of plasma cells or may play a role in plasma cell proliferation. A number of therapies have been tried to affect angiogenesis, including thalidomide, endostatin, ImiD (e.g. Revimid, ACTMID), 2ME2 (2-methoxyestradiol) and VEGF (Vascular Endothelial Growth Factor) inhibition. Various immunotherapies are also being tested.

Immunotherapy and Residual Disease

- ◆ DLI (donor leukocyte infusions) has an anti-myeloma effect
- ◆ CD4 enrichment may reduce the GVH (graft versus host) effect without compromising the anti-myeloma effect
- ◆ Idiotype vaccine disappointing but the development of response of Helper T cells of the immune system correlate with clinical response.
- ◆ Myeloma antigen and whole cell immunization studies underway
- ◆ Activation of CD40 (a protein on the surface of B and tumour cells) may assist the Helper T cell response, at least in the test tube (*in vitro*)
- ◆ Dendritic cell approaches being used
- ◆ Il-12 (interleukin 12) produces responses that may enhance TH1 cell generation (Helper T cells) in patients
- ◆ Residual disease by flow cytometry or molecular genetic testing detects one in every 10,000 to 100,000 cells

Agents other than bisphosphonates may also be helpful in treating bone lesions. We are learning that bone metabolism in myeloma is affected by a variety of factors. MIP- α (macrophage inflammatory protein) and VEGF (vascular endothelial growth factor) are very important in the breakdown of bone and has been found to be highly upregulated in myeloma cells. These elements are being targeted by thalidomide ImiD therapies.

A protein called RANK⁴ is found on osteoclasts⁵ and controls their activation. Proteasome inhibitors such as PS341 attack this mechanism. Having agents such as PS341 (Velcade) that attack both the myeloma cells and the osteoclasts could be helpful in the future.

The main regulator of osteoclasts is osteoprotegerin (OPG). This compound, which was only discovered four years ago, blocks the interaction between osteoclasts and RANK or TRANCE.⁶ We turn over our skeletons about every couple of months and we do that by resorbing bone with osteoclasts and laying down new bone with

⁴ Receptor Activator of NF-KD (nuclear factor kappa b)

⁵ Osteoclasts are large cells responsible for the breakdown of bone.

⁶ A tumor necrosis factor cytokine that is responsible for the production and survival of osteoclasts.

osteoblasts. This has to be very finely regulated and apparently OPG is one of the main regulators.

New bone disease modulators include:

- ◆ IL-1 β antagonists to block IL-6 effect
- ◆ OPG (currently in Phase I testing)
- ◆ Inhibitors of RANK-L (RANK ligand)
- ◆ Antibodies to PTH-rp (parathyroid hormone-related protein)
- ◆ Integrin⁷ inhibitors
- ◆ Statin drugs for BMP2 (bone morphogenetic protein 2) inhibition

One of the more encouraging aspects of myeloma is the number of new agents in development and being tested.

New Agents for Myeloma

- ◆ IMiDs -- thalidomide derivatives
- ◆ 2ME2 – antiangiogenesis agent
- ◆ VEGF receptor antagonists/anti-angiogenesis
- ◆ FTI inhibitors – *ras* protein oncogene inhibition
- ◆ IGF (Insulin like Growth Factor) pathway inhibition
- ◆ PS341 (proteasome inhibitor NFkB and combinations)
- ◆ Rituximab for CD20+ myeloma
- ◆ Other monoclonal antibodies (e.g CD38)
- ◆ IL- β inhibitor/receptor antagonist
- ◆ Enbrel® TNF α (tumor necrosis factor alpha) inhibitor
- ◆ Zoledronic acid and osteoprotegerin
- ◆ Gene therapy

There is good potential for treatment during the plateau phase when the myeloma tumour growth is low. Clinical trials for plateau phase myeloma include:

- ◆ Immune Approaches
 - ◆ Vaccines such as DNA vaccines and dendritic cell manipulation
 - ◆ Donor lymphocyte infusion after allogeneic or mini-allogeneic transplant
 - ◆ Interleukin-12 and MPL
- ◆ Thalidomide + prednisone

⁷ Integrins are a superfamily of cell surface proteins that are involved in binding cells to extracellular matrix compounds.

The interaction of the myeloma cell with its environment is very complicated. The end result is that the myeloma cells make factors that stimulate the bone marrow to release growth factors and knock out T cells that could fight against the myeloma cells, as well as grow new blood vessels (angiogenesis). Thalidomide targets all of those mechanisms: the bone marrow stroma⁸ cells, the angiogenesis mechanism and the T cells. Here's a drug that was literally sitting on the shelf and now has been found to have this incredible effect in myeloma.

Following are results of single-agent thalidomide trials in recurrent or refractory multiple myeloma. In this table, response rates for the Singhal and Barlogie trial represent a 50% decrease in M proteins.

Single-Agent Thalidomide in Recurrent/ Refractory Myeloma

Study	Patient Population	Dose	No. Pts.	Response Rate
Singhal	Refractory	200-800 mg/d	84	32%
Barlogie	Advanced, refractory	200-800 mg/d	169	30%
Grosbois	Advanced	200 –400 mg/d	121	41% minor response

In recurrent or refractory multiple myeloma, thalidomide has also been combined with other therapies. Results from the major trials are as follows.

Combination Thalidomide Therapy in Recurrent/Refractory Myeloma

Study	Patient Population	No. Pts.	Therapy/ Dosing	Response Rate
Munshi et al	Previously treated	43	DT-PACE (thalidomide 400 mg/d)	69%
Coleman et al	Relapsed	13	Thalidomide 50-200 mg/d, dex 40 mg q2wk, clarithromycin 250-500 mg bid	100% ¹
Weber	Refractory	47	200-800 mg/d + dex 20 mg d1-5, 15-18	52%
Palumbo	Relapsed	77	100 mg/d + dex 40 mg d1-4	66%

¹ As measured by a reduction in IG spike of 50% or more

⁸ Stromal cells are connective tissue cells found, among other places, in the loose connective tissue of the hematopoietic system (the system for making red blood cells).

The bottom line here is that when you combine steroids and thalidomide you get response rates better than with either agent used alone.

Thalidomide in Previously Untreated Myeloma

Study	No. Pts.	Dose	Response Rate
Single-Agent Therapy:			
Weber et al	26	200-600 mg/d	35%
Rajkumar et al	16 ¹	200-800 mg/d	36%
Combination Therapy:			
Rajkumar et al	50	Thalidomide 200 mg/d, dex 40 mg days 1-4, 9-12 and 17-20 (odd cycles)	64%

¹ Smoldering or indolent multiple myeloma

Currently we are conducting trials using thalidomide and dexamethasone in combination versus dexamethasone alone to see if the combination increases the response rate you get from dexamethasone alone. We're certain it will but there may be other toxicities, such as increased blood clots in the veins, that we need to consider.

The major toxicities of thalidomide are nonhematologic, that is to say, do not involve the blood or blood-forming system. Side effects or toxicities include constipation, fatigue/sedation, skin toxicity/rash and peripheral neuropathy (which usually takes a while to develop and tends to develop more in older folks and those who have been previously exposed to vincristine). About 8-14% of people may develop deep vein thrombosis⁹. We also sometimes see deep vein thrombosis in patients who are treated with VAD but it's an open question as to whether they should be treated with blood thinners. The side effects of thalidomide are manageable if you change the dose or stop treatment. Neuropathy, however, can be permanent, which is why we monitor patients very carefully.

There's a real paradigm shift because of thalidomide. For example, here's a patient who was under observation for smoldering myeloma whose M protein began to increase. He was started on thalidomide and you can see the dramatic drop in the M protein which persisted for five years.

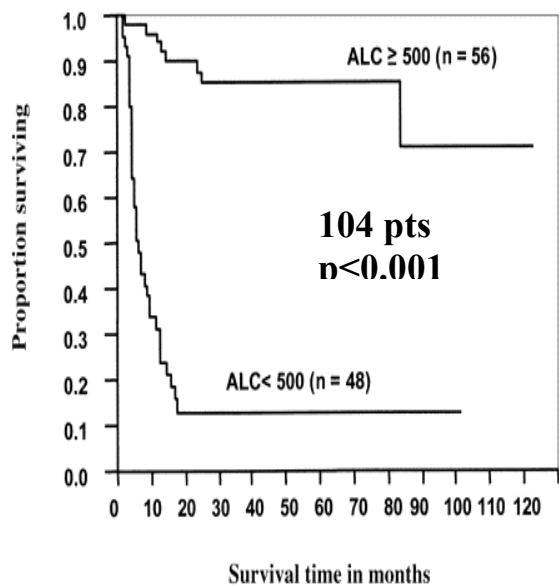
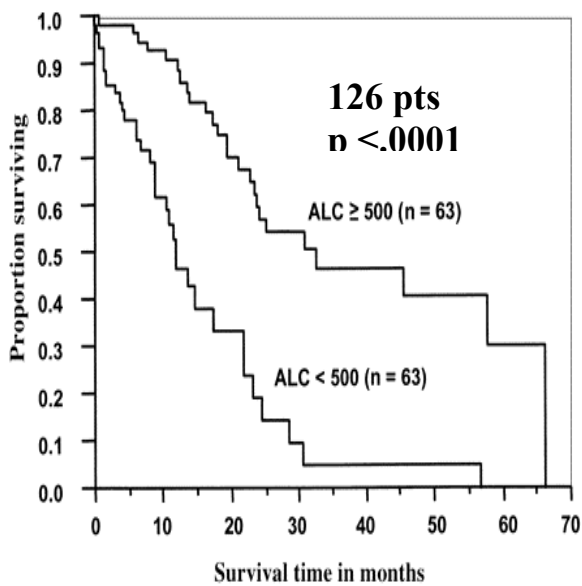
⁹ The formation of blood clots (thrombi) in the veins.

The other paradigm shift is with PS341 or Velcade. Here we have a patient who I've been following for four and a half years. He had sort of a smoldering disease but when myeloma became active, we started him on VAD chemotherapy. It had no effect and his M protein continued to rise. He had a transplant but the response was sub-optimal. We then tried thalidomide and it didn't have much effect; it was only when we added dexamethasone that we got an effect. However, as I discussed earlier, you can't give the combination of dexamethasone and thalidomide for very long because of the side effects. We had to cut down the dose because of side effects and the M protein escaped and went up again. We had to stop the dexamethasone and thalidomide, his M protein continued to climb and we tried PS341. He got the best response ever with PS341 alone. A year and a half later, he is still doing very well. This is really shifting our paradigm about treatment. We think the response rate will be about 35% and we're trying it on high-risk patients with the idea that maybe patients who don't respond well to transplant may respond to PS341.

Another therapy developed by Steve Russell in our gene therapy group at Mayo is a measles virus effect. The measles virus kills cells by adhering them together. He has shown in culture that a strain of the measles virus can infect myeloma cells and prevent their growth by fusing their cell membranes. In an animal model, when measles cells were given with, or after, tumour cells, the tumours didn't grow. This new type of gene therapy is something we'll see more of in the future.

Here is an example of why we are so interested in pursuing immunotherapy. The following graphs show the outcome of patients with myeloma who received autologous stem cell transplant, based on their lymphocyte¹⁰ counts.

Lymphocyte Recovery After Autologous Stem Cell Transplant -- Markovic



¹⁰ Lymphocytes are white blood cells that fight infection and disease.

You can see that if you have good lymphocyte counts, 15 days after your transplant you're going to be doing much better than someone with a low lymphocyte count. A trial at John Hopkin's is looking at ways to take lymphocytes out before the transplant, incubating them with substances that increase their number and activation, and giving them back to the patients.

There are also fraudulent therapies out there. One of my colleagues at Mayo, Morie Gertz, has said:

“Unscrupulous practitioners are becoming increasingly sophisticated in their presentation of fraudulent therapies to the public at large.... This results in a tremendous burden for the patient (and their families). Not only do they have to cope with the fact that they have a malignancy, but they have the added burden that (a failed therapy) is their fault.”

I have a folder full of examples of fraudulent therapies. The old saying, “Ask your doctor,” is probably a good idea. There are some things that are relatively harmless that you might try. What raises a red flag for me is when there is one doctor or practitioner doing one therapy for all diseases. There's something wrong there.

To conclude, myeloma is a heterogeneous disease defined not only by cytogenetic and molecular genetic changes but by microenvironment changes. Microenvironment changes can effect myeloma cell growth. Targeting the cell signaling, rather than higher dose therapy, are really the new frontier of myeloma therapy. Immunotherapy still holds promise but requires new technological advances and clinical trials.

Almost a hundred years ago, Sir William Osler¹¹ commented on the importance of understanding that each patient, is different. He said, “It is much more important to know what sort of patient has a disease than what sort of disease a patient has.”

That's my segue into a story about one of my patients, Mr. “B”. Mr. B. was an elementary school principal who recently retired after contracting amyloidosis¹²— and who exemplifies the principle of knowing what is most important in life. Patients with cardiac involvement, such as he had, usually live only six months but at this point he has been alive for about four years. The kids at his school made up this story book about him, illustrating what they remembered about him. They remembered the feel

¹¹ Sir William Osler (1849-1010) was a Canadian born and trained physician who has been described as “the best known physician in the English-speaking world at the turn of the century” and “the most influential physician in history.”

¹² A disease which sometimes complicates or overlaps myeloma and sometimes occurs on its own. Amyloidosis is a common complication of diseases associated with disturbance of the immune system.

of his hand when they shook their hands, it made them feel special and important. They remembered that at the end of each day he stood outside, watching the kids find their buses and sometimes helping those who were lost. Parents picking up their kids talked to him too. The kids admitted that they really kept him busy. He knew his responsibilities and knew that sometimes he had to talk to the kids about things they had to correct.

After he retired, the kids didn't remember that he shuffled papers or made major contributions to the school system. What they remembered was that he was in the lunch room all the time, his handshakes, that he went out to the buses. One kid wrote that his mom said that when you miss people, you only need to think of your memories of them and they can be right there with you again. People you care about are in your heart and never really go away.

The kids remembered him for who he was, not what he did. They pictured him in retirement sitting in a boat with his fishing pole, with a smile and a wave, happily fishing. Although he retired, he didn't forget to take care of himself.

In the end what matters most is taking care of yourself, caring for other people, honouring your responsibilities, balance and growth.

A patient sent me this last week, and I wanted to share it with you. It's an exercise plan for seniors, although it could be used for anyone. It's a secret for building arm and shoulder muscles. Following it three days a week works well. Begin by standing outside behind the house and with a 5-lb. potato sack in each hand, extend your arms straight out to your side and hold them there as long as you can. After a few weeks, move up to 10-lb potato sacks and then 20-lb potato sacks. Keep at it until you get to where you can lift a 50-lb potato sack in each hand and hold your arms straight for more than a full minute.

Next ...start putting a few potatoes in the sacks, but be careful not to overdo it!

Questions & Answers

Q: Should you centre your life around your myeloma?

A: I think it's important that myeloma not be the centre of your life. There are some exceptions, such as Kathy Giusti of Multiple Myeloma Research Foundation and Susan Novis of International Myeloma Foundation but they are doing it for others.

Q: Do you believe in the power of positive thinking for myeloma?

A: I'm a student of these things but I'm not a disciple. We've all seen examples where patients are alive because of it. I was reading a book by Bill Moyers¹³ which

¹³ Bill Moyers. Healing and the Mind.

was given to me by a patient, and in the first few chapters you see that some of this is cultural. We're not necessarily a body with a spirit but a spirit with a body. Whether positive thinking can affect your myeloma is unknown. There haven't been any real study of such things as the effects of qi gong (need to reference this), a form of meditation on the immune system and designing these sorts of study are difficult. I do, however, object to those who argue that individual is totally in charge. Bill Moyers is pretty balanced in that respect but there are others who are pretty unbalanced.

Q: Are tandem transplants beneficial in extending life?

A: The results of the French study of tandem transplants show improved event-free survival in the patients who had tandem instead of single transplant. The extension of survival was in the order of 8 months and the results were statistically significant at the time point chosen. I have some problems with the trial, however. The results were analyzed four times during the course of the study and showed significant differences at some points and not at others. Which analysis was correct? Each time you analyze your data, you lose statistical power. If you repeat the analysis several times, you increase the odds that you will statistically find a difference even though there isn't one in reality. Fortunately, there are two or three other trials on tandem vs. single transplants in progress. There have also been a couple of negative trials reported but the results are early. At the Mayo Clinic we try to harvest enough stem cells for two transplants but we're not doing tandem transplants. There's some evidence that an early versus a delayed transplant has about the same effect in terms of extension of survival as a up front transplant. Perhaps an early and late are as good or better than a tandem transplant, we don't know yet.

Q: How should you choose between the different trials underway?

A: In some cases, participating in a trial can be beneficial for your treatment but in other cases, it may be totally an altruistic decision. If you've been through some standard therapy options, or for other reasons, you may want to try new therapies in trial. Deciding whether or not to participate is a personal choice. Few can afford to travel great distances to participate in a trial. Choosing a trial to participate in is a very personal decision. Trials are held because we don't know enough about a new therapy, such as whether or not it will be effective, or what the correct dose should be, or whether it might be better than a standard therapy

Q: Do we have any new information on the causes of myeloma?

A: There are a number of potential areas to look at, including radiation, toxic damage from chemical, viruses and familial inherited tendency. Myeloma is a rare cancer. It occasionally happens twice in a family but rarely. We've also known twins in which one develops myeloma but the other doesn't. Some cases which have appeared to be linked to chemicals have often turned out to be random clusters. Of the various chemicals, none has a clear relationship to myeloma. Almost everyone can find

some sort of toxic chemical exposure at some point in their life. There has been a great deal of literature both pro and con about the role of viruses in myeloma but nothing has been proven yet. It was once thought that radiation, such as the atomic bomb in Hiroshima, caused myeloma but subsequent studies found the initial studies were flawed. Surveys can give you ideas about what might cause myeloma, but can't give you proof.

Q: Is there a relationship between non-Hodgkins malignant lymphoma and myeloma?

A: Both are malignant diseases of a common cell of origin in the marrow, the B-cell. Some people have developed one disease and then the other or both diseases simultaneously. There doesn't seem to be any true tendency for patients with malignant lymphoma to develop myeloma and it is difficult to identify whether there is a common cause. It's not something you expect and could be a coincidence.

Q: What are the adverse side effects of PS341?

A: There is a narrow therapeutic index for PS341 in many patients. There is a fine line between the dose that causes beneficial effects against the myeloma and that which causes toxic effects for the patient. It's not a simple drug to administer. Side effects can be a weakness and malaise that is very debilitating, low platelet counts, and an immunosuppressive effect that can result in serious and unusual infections. Like all chemotherapies, PS431 is really a self poison so you may have to put up with the side effects to reap the benefits. It can also aggravate neuropathy, especially if the neuropathy was caused by thalidomide.

Q: Can you use tetracycline or other antibiotics as myeloma therapy?

A: No. The closest thing to this is Biaxin® (clarithromycin). Initially studies of Biaxin saw a response rate of something like 30% but it turned out that most of these patients were also getting steroids for so-called "flare reactions." So the question is, did the response come from the Biaxin or the steroids? There have been trials in which the Biaxin may have worked but others in which it has not. I regard tetracycline as a broad-base antibiotic with no anti-myeloma effect.