

Future Directions in the Treatment of Multiple Myeloma

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It is energizing for physicians to meet with groups such as yours that are so interested in what we're doing and the progress we're making. In the first part of this talk, I want to discuss the standard treatment for multiple myeloma. In the second part, I'll talk about some of the new biologies and treatments. Finally, we'll also talk a bit about life with this disease.

In multiple myeloma, there's an abnormal plasma cell clone that proliferates at the expense of the other, healthy cells in the bone marrow. This clone produces an abnormal protein (a monoclonal immunoglobulin) that can be seen in the blood as a Monoclonal Spike or M-spike. You can measure the monoclonal protein either by looking at the total M-spike or looking at the particular type of monoclonal protein being produced, such as immunoglobulin A (IgA), E (IgE), G (IgG) or M (IgM). Or you can examine the blood serum or the urine for Kappa (κ) or Lambda (λ) free light chains.

The precursor of this condition is referred to as Monoclonal Gammopathy of Undetermined Significance, which at the Mayo Clinic we call MGUS. MGUS was first described by Dr. Kyle's initial series of 241 patients. In these patients, there was less than 10% marrow plasma cells, no evidence of multiple myeloma and no anemia, renal insufficiency or bone lesions. About 15% of the patients eventually went on to develop multiple myeloma or some other serious disorder, a rate of development of about 1% per year. Currently, we have no way of predicting which patients with MGUS will progress to active myeloma and which will remain stable. We think that 72% of patients with myeloma have a pre-existing MGUS. Using the sensitive test for free light chains in the serum, there's probably a monoclonal protein in even more. I suspect everyone who has myeloma probably has this precursor condition MGUS that eventually evolves into active myeloma.

In active multiple myeloma the marrow plasma cells increase and there are higher and progressive levels of M-proteins. Two-thirds of patients will have bone

¹ Disturbance in the production of proteins produced by plasma cells that help fight infection.

lesions, two-thirds anemia, one out of six hypercalcemia (high levels of calcium compounds in the blood) and one out of five renal insufficiency. The important thing to remember is that a third of patients don't have bone lesions. Bone lesions, anemia, hypercalcemia and kidney failure are not absolutely necessary for the diagnosis.

There's increasing recognition that some patients' myeloma progresses in a very sneaky sort of way. I call them transition states between MGUS and myeloma. The terms we use to describe them, and which will soon be published in the British Journal of Haematology, are *smoldering*, *indolent* and *asymptomatic* myeloma. The criteria for these states are greater than 10% plasma cells in the marrow or greater than 3 grams of monoclonal protein in the serum. From these states, patients can go on to develop active multiple myeloma.

It's important to recognize the smoldering, asymptomatic and indolent forms of multiple myeloma. Doing so will help avoid unnecessary chemotherapy, which can sometimes damage the bone marrow. We also want to look at patients in these stages as possible opportunities for studying the new biologic therapies.

There are lots of faces of multiple myeloma and it can present in many different ways. In some folks, myeloma is not so bad but for others it can be pretty ugly. You can't necessarily tell by looking at the patient how the myeloma will go, which is why you need new biological tools. The bone marrow Plasma Cell Labeling Index (PCLI) is probably the most practical and established test that we have. I've been using it since 1977. It's clear that if you have a higher growth rate of the plasma cells, the patient will be more likely to have the active form of the disease and to have a worse prognosis. Conversely, a lower growth rate corresponds with a better prognosis.

PCLI is useful even when there is a low percentage of plasma cells. At the Mayo Clinic we've done studies to show it's the best discriminant of myeloma that we have and can distinguish multiple myeloma from asymptomatic conditions such as MGUS or smoldering myeloma. The test is useful even with a low percentage of marrow plasma cells. To do the test, we look down a fluorescent microscope at plasma cells stained with a light chain dye. The colour of the nuclei will show you whether they are proliferating. In a typical day, I may read about twenty of these tests, both samples from Mayo patients as well as samples mailed in from other centres.

Looking at circulating plasma cells is another test we can do on the blood. The test is relatively simple to do for an experienced laboratory such as mine, but more difficult for an average laboratory that may do only a few a year. The test is performed on peripheral blood and results are usually available in a day. About half of patients with myeloma have excess circulating myeloma cells in the blood.

In about 10% of patients, if you look at the cells you find plasmablastic cells². Typically, they will also have other features that suggest their myeloma may be more aggressive, such as a higher PCLI and sIL-6R (serum interleukin 6R), more frequent *ras* protein mutations, higher calcium and β 2M (beta 2 microglobulin) levels, and lower hemoglobin and albumin.

Once the diagnosis of myeloma is made and it's determined that treatment is needed, there's a wide variation of expected life spans. We are just beginning to be able to measure this and newer techniques are in development that will help us.

Median¹ and 5-year Survival Central Lab Risk Groups: PB, PCLI, β2M			
	Number of people	Median³ Survival	% who were alive at end of 5 years
Low Low β 2M (< 4) & PCLI	93	5.5 years	52%
Intermediate	217	3.9 years	36%
High			
High β 2M & PCLI	77	2.4 years	13%
PB (PCLI<1)	18	2.3 years	11%
PB (PCLI \geq 1)	17	1.1 years	0%

Newer techniques that may help us evaluate the prognosis of patients include cytogenetics.⁴ In about 20% of patients, the cells are proliferating and you can look at their karyotype⁵ or chromosome spread. Using a technique called FISH (Fluorescent in Situ Hybridization) you can use a red or green probe to look at the chromosomes. You should have two of each chromosome. But for chromosome 7, the myeloma patient often has a third chromosome (trisomy-7). Or there may be translocation of one piece of chromosome to another. In myeloma, one of the most common translocations is between chromosome 11 and 14 (fusion 11:14). Both trisomy 7 and fusion 11:14 are associated with more favourable outcomes.

FISH can also show you, even in those people without cell proliferation, if there is a loss or deletion of part of chromosome 13. A problem with chromosome 13 is associated with a more unfavourable outcome than fusion 11:14 but is not as bad as some of the other translocations and other chromosome abnormalities. In short,

² A plasmablast is a precursor of a plasma cell.

³ A median is the number that divides a group in half. For the low group, for example, it means half of the people died before 5.5 years and half after 5.5 years.

⁴ Cytogenetics is the study of the structure of chromosomes.

⁵ A karyotype looks at the chromosomes of an individual cell, arranged in pairs and sorted by size.

we think FISH cytogenetics is going to be very useful for segregating out different kinds of myeloma. This will help us decide what to recommend for treatment.

I'd now like to talk about standard treatments of multiple myeloma, what is accepted by virtue of being tried, true and repeatedly proven. We'll be looking at four different phases: (1) smoldering, indolent or asymptomatic myeloma; (2) active myeloma; (3) plateau; and (4) relapse.

Initial Treatment for Smoldering, Indolent or Asymptomatic Myeloma:

- ◆ Observation
- ◆ Bisphosphonates
- ◆ Erythropoietin
- ◆ Clinical trials with biologicals or new agents

It's fair to say that for the smoldering and indolent forms of the disease, observation is the standard of care. These patients may become a little anemic but may not yet have bone lesions or kidney failure. The physician and patient may not be anxious to start chemotherapy at this point. At the Mayo Clinic, we have patients who have done well for years with just erythropoietin support to maintain their hemoglobin and prevent anemia. Of course, there are always exceptions. Even though erythropoietin is aimed at stimulating the production of red blood cells, its receptor is also found on myeloma cells. I had one patient whose myeloma got worse when taking erythropoietin. We had to stop the treatment and then the myeloma stopped getting worse temporarily.

Bisphosphonates are a proven and recommended treatment for patients with bone lesions. The problems with this therapy include the expense, inconvenience, and the risk of damaging the kidneys. In general, we don't recommend bisphosphonates for smoldering or indolent myeloma but we're anxious to start clinical trials where we can see if there's benefit and what the outcome may be. At this point, we think the likelihood of benefit in any individual patient in these stages is probably very small.

Standard Treatment Options for Myeloma

- ◆ Patients more than 70 years of age
 - ◆ All melphalan and prednisone- containing regimens are equivalent
 - ◆ Addition of interferon (INF) and high dose Cytoxan (CTX) may result in more Complete Response (CRs) but overall effect is debatable
- ◆ Patients less than 70 years of age
 - ◆ Principle of treatment planning is to not choose a treatment that eliminates other options you might want to consider later on

- ◆ Peripheral stem cell transplant associated with low mortality rates and higher CR rates than standard chemotherapy. However, there is a continuous relapse rate so better pre-harvest treatment and maintenance is needed. Initial debulking therapy needs to protect normal stem cells (limit number of cycles of VAD, dexamethasone or thalidomide). Debatable issues include: early vs delayed transplant? Double vs single transplant?

In active multiple myeloma the standard treatment for patients above the age of 70 is melphalan and prednisone. There are a number of melphalan and prednisone regimes. The use of interferon and use dose Cytoxan is being tested and may result in more complete responses. But I think for the patient above the age or 70, or the patient who is not a candidate for transplant, melphalan and prednisone should be the standard therapy.

What about patients who are under the age of 70 and eligible for transplant? Before making any treatment choices, you have to realize that any choice you make now may affect your options down the road. It's important to think about that and not eliminate any options that you might want to consider later. Months and months of melphalan and prednisone can damage the stem cells and make it impossible to collect them for transplant. So the younger patient who may want to consider transplant in the future will need some sort of other pre-harvest treatment. The primary preharvest treatment at this point is a limited cycle of VAD (Vincristin, Adriamycin and Dexamethasone), but I think dexamethasone is just as effective and results in less complications because it is an oral medication. I'll talk about the combination of thalidomide and dexamethasone in another section of this talk.

For patients under the age of 55, allogeneic transplant – a transplant from a matched sibling donor or a matched unrelated donor – is a possibility. The harvested donor cells are used to restore normal blood cell counts after high dose chemotherapy. This is used primarily for younger patients with high-risk myeloma, as it is associated with a high mortality rate due to the graft vs host response. During earlier studies, the 100-day mortality rate was 41% but it's now down to about 30%. So it's not a very attractive treatment except for someone who has very few options. A continuous pattern of relapse can still occur after transplant. Obviously, timing is very important when considering this option.

Despite the risks, I've also had patients who have been virtually cured by allogeneic transplant, something you can't say about other treatments. Allogeneic transplants induce a graft vs myeloma effect in which the donor cells reject the myeloma cells of the host. The treatment has potential and shows that some sort of immune therapy may be effective in myeloma. How can we make the treatment less toxic? Perhaps, instead of giving very high doses of chemotherapy, we could try suppressing the immune function of the bone marrow, which could allow the donor cells to take.

A study of patients under the age of 55 who received mini-allogeneic transplants used the donor cells to establish an immune reaction against the myeloma, such as occurs in allogeneic transplant. There was a lower mortality rate than standard allogeneic transplant because there was a lower graft vs host effect. However, the graft vs myeloma effect was uncertain. Also, there was a late graft vs host effect that developed a year or so after the mini-allogeneic transplant. It was basically like acquiring another illness, affecting the liver, the gut and the skin. So we have to find a better way of treating the lymphocytes that are being infused so they kill the myeloma cells instead of damaging the host cells. A lot of research is required.

Plateau/Maintenance Treatment for Myeloma

- ◆ Observation only
 - ◆ Alternate day prednisone therapy (needs confirmation)
- ◆ Interferon therapy (longer remissions, significant toxicity, survival prolongation is marginal, relapses more aggressive)

What's the standard treatment after you've had a transplant or melphalan or prednisone, and you're in remission at a plateau phase? The standard treatment is observation only. The Southwest Oncology Group showed longer survival in a group of patients who received alternate-day prednisone therapy. However, there are some questions as to whether the patients who got the prednisone were the ones who had already been shown to be responsive to steroids. So it's not clear that this is useful. After about a year or two of alternate day prednisone therapy, you get a lot of side effects involving the bones and muscles, so you need to take into account the complications. That's why we tend to look for opportunities to do clinical trials in these patients and learn more about these types of treatment.

Interferon therapy has been shown to be somewhat effective in prolonging remission but the relapses after remission come more aggressively and the survival is actually the same or very similar. The Myeloma Trialist Group assembled all of the interferon trials and found a very slight benefit of about 2% long-term survival in the interferon group. However, it was agreed that this benefit is probably not worth the grief of the treatment. Almost every patient that was on interferon initially went off treatment by about 2 years. Most patients were unable to tolerate it for even that long.

Supportive Care for Myeloma

- ◆ Pamidronate vs. Zometa
 - ◆ Erythropoietin
- ◆ Antibiotic prophylaxis (dexamethasone)
- ◆ Acid blocker therapy (dexamethasone)

- ◆ Fluids
- ◆ Avoid high dose vitamin C
 - ◆ Increase activity
- ◆ Orthopedic measures (vertebroplasty or kyphoplasty, other pain measures)
 - ◆ Local radiation therapy

Part of standard treatment for myeloma is supportive care. Erythropoietin is very useful for patients with anemia. The only question is where the hemoglobin should be maintained. The goal should be to maintain the hemoglobin at a level where the patient feels the best. For patients on dexamethasone, antibiotic prophylaxis and acid blocker therapy is important. Fluids are very important for myeloma patients. We always emphasize that patients drink about 3 litres or quarts of water a day, especially if they have Bence Jones proteinuria or free light chains in the urine. We also recommend avoiding the use of high doses of vitamin C. I've seen four patients develop renal failure on high dose vitamin C. It can acidify the urine. If you acidify milk, for example, the protein curds. This is what can happen in the renal tubules. The ascorbic acid of vitamin C basically "curds" the protein in the urine, blocking the tubules and leading to kidney failure. That doesn't mean that you shouldn't eat oranges or take something like 500 milligrams of vitamin C a day. It means that you shouldn't take enormous doses.

Increased activity is also important for myeloma patients. Orthopedic measures such as vertebroplasty or kyphoplasty are other supportive measures for myeloma patients. We try and save local radiation therapy as a last resort.

How can a patient choose between different therapies? To begin with, it is important to think about how your current decisions will effect your future options. For example, melphalan may eliminate the possibility of harvesting stem cells in the future. You need to know the risk of your particular stage of myeloma with either observation or standard therapy. If the myeloma is not progressing or is smoldering or asymptomatic, maybe you shouldn't undergo any treatment. And consider participating in a clinical trial. It's always at least as good as standard care, provides close monitoring, may benefit others and it may mean that you will be among the first to benefit from a new therapy.

I'd now like to give you three examples of patients with asymptomatic or smoldering myeloma who I have seen in my practice. I think they illustrate the importance of observation therapy.

Patient #1: Smoldering Myeloma: Caution before Treatment

- ◆ 37-year-old woman
- ◆ Jan/96: gammaglobulin 3.2; IgG_K M-spike 2.8 IgG level 3550, hemoglobin 11.7; repeat 10.9; β2M 1.5; normal bone survey; bone marrow 15-20% plasma cells

- ◆ Mayo Clinic: Bone marrow 20% plasma cells, PCLI 0.0, no circulating plasma cells. Diagnosed with smoldering myeloma and observed for 4 years with no progression.
- ◆ 1999: Incidental discovery of osteoporosis, treated with pamidronate 90 mg monthly; bone density normal one year later

This woman was diagnosed with myeloma and her protein levels were high and the bone marrow had plenty of plasma cells. She had an identical twin and three centres advised allogeneic transplant. She came to the Mayo for a fourth option. We found that although there was 20% plasma cells, that the labelling index was zero and there were no circulating plasma cells. We recommended observation. She's been observed now for six and a half years with no progression. Since that time, she's given birth to another child and founded the Multiple Myeloma Research Foundation.

In 1999 a bone density scan found she was osteoporotic. She continued with pamidronate and a year later the myeloma hadn't changed but the bone density was normal. That's very unusual with osteoporosis due to myeloma so I suspect she just had osteoporosis.

Patient #2: Smoldering Myeloma: Long Follow Up

- ◆ 53-year-old female
- ◆ 1975: Came to Mayo Clinic with gamma globulin 3.0, IgG_K M-spike 2.6, IgG level 3200, hemoglobin 11.0, β₂M; creatinine, calcium and bone survey normal; marrow 30% plasma cells, PCLI 0.0
- ◆ Active observation with monitoring of M-protein 13 years before bone lesions and back pain indicated need for treatment
- ◆ Treated with melphalan and prednisone, died at age 79 from progressive and resistant myeloma

Here's another example of why you should just observe an asymptomatic patient. You can get very long follow-up on some of these patients. This patient came when I was a resident at the Mayo Clinic in 1975, doing what my daughter does now (my daughter is a Fellow in Hematology at Mayo). I saw this patient and when I walked into the room she seemed shocked to see a resident because she was expecting to see Dr. Kyle. I asked, "Were you expecting to see an older physician?" and she said she was. I actively observed her for the next thirteen years with no treatment for her myeloma before she developed active disease. She died last year at age 79 from progressive and resistant multiple myeloma. But shortly before this, we had a conversation and I remember what she had said to me in 1975 and I said to her, "You finally got the older physician you were looking for years ago."

Patient #3: Smoldering Myeloma: Clinical Trials

- ◆ 40-year-old male
- ◆ 1992: IgG_K M-spike 2.0, no bone lesions or circulating plasma cells, β2M 1.4, marrow 15%, PCLI 0.1%, 4 years later M-spike 2.4, marrow 13% plasma cells; however PCLI 1.4%, small lucencies on bone survey, started Aredia 90 mg.
- ◆ 1997: M-spike 2.5 g/dl, marrow 20% plasma cells, PCLI 0.2%, bone lesions stable, Aredia to twice monthly; one year later M-spike to 3.1, marrow angiogenesis
- ◆ 1999: M-spike to 4.6, IgG 6600, marrow 30% plasma cells, bone lesions same; hemoglobin 12.4, thalidomide started and increased to 800 mg/day
- ◆ Current status thalidomide reduced to 200 mg/day, M-spike 1.5, IgG 1750, hemoglobin 15.0; marrow 5% plasma cells, PCLI 0.4, stem cells collected

Here's another example of how diagnosing an asymptomatic patient opens the opportunity for clinical trial and how that can benefit a patient. This is a patient with clear-cut myeloma, started on Aredia because he had very tiny lucencies on the x-ray. Then he became asymptomatic so we observed. The M-spike went up and at one point his bone marrow went up to 30% plasma cells and his hemoglobin dropped from the 15 range to 12.4. We started thalidomide on a clinical trial and increased to 800 mg. a day without any effect on his golf game. Currently, his thalidomide has been reduced to 200 mgs a day, his M-spike is low, his hemoglobin is up to the 15 range, his bone marrow plasma cells are down to 5%, his labelling index is low and his stem cells have been collected. This is a person who has really benefited from joining a clinical trial.

Questions and Answers

Q: Has melphalan and prednisone been compared to Cytoxan (cyclophosphamide) and prednisone?

The two regimens have not been compared head-to-head but there are probably roughly equivalent in their efficacy. I've seen patients who failed the standard regimen melphalan and prednisone every six weeks (there's another regimen of every four weeks) and whose disease was brought under control by switching to a simple regimen of daily Cytoxan and prednisone twice a week (which is a Canadian regimen I like). If the disease or relapse is relatively indolent, I think they can respond well to the oral prednisone.

Q: Description of a patient who responded to an agent developed at McGill.

This question raises the issue of the need for clinical trials to study agents. I've had patients who have had very high levels of proteins who return with improvement without apparently doing anything. We don't know the actual incidence of

spontaneous improvements in myeloma. We know that in certain types of lymphoma it's as high as 20%. I know it happens in myeloma as well but we don't know how often. This shows why trials are so important to determine scientifically what is happening and why.

Q: How can we combine new treatments such as thalidomide with standard treatments such as stem cell transplant?

I encourage people to get their stem cells harvested early, rather than to take several years of thalidomide before deciding to try a transplant. There's some evidence that thalidomide can damage stem cells. In patients who have only taken thalidomide for a few months, we think a rest period of two to four weeks is enough to allow us to collect the stem cells. But we don't know what a year or two of thalidomide will do to the stem cells. If you're collecting stem cells, you don't want to collect half, you want to collect all you can possibly get. If you can collect enough for two transplants, you want to be able to do it.

Q: Potential of kidney damage associated with Aredia and Aredia alternatives?

A: Kidney damage is rare and it can be picked up by careful monitoring. Zometa is another possible treatment, but it can cause kidney damage in a small number of cases.

Q: When you're in plateau phase after melphalan and prednisone, how do you know when to start treatment again?

A: This is where the monitoring of the monoclonal protein is very important. There are some patients who have monoclonal spikes in the serum that can be monitored. If you're in a plateau and your monoclonal spike is 2 grams and before treatment it was 6 grams, you know that when you get back to 6 grams you'll be in trouble. You want to treat before you get back there. I usually wait until the monoclonal protein is about half of what it was prior to treatment. The same is true of the urine.

Q: How frequently should you be monitored when you're in plateau phase?

The monitoring frequency depends upon the physician's judgement. I've got some patients who I thought their disease was more active and I monitor monthly; others whose disease seems rather indolent I monitor every three months. I've even got some patients who I've seen for ten years and monitor every six months. It varies according to the aggressiveness of the disease. At the Mayo Clinic, we're beginning to monitor all of our patients with the serum free light chain. It's helpful as no patient enjoys having to collect 24-hour urine samples. We don't yet know if the serum free light chain test will be a substitute for the 24-hour urine sample but we think it may be helpful. At this point, it needs to be proven and published.

Q: Should you avoid citrus fruits because of the vitamin C?

A: No studies have been done to show what dose of vitamin C is harmful. You don't have to limit the number of oranges or grapefruits you eat, just avoid massive doses (e.g. 4000 mg/day).

Q: Does VAD chemotherapy restrict you from other treatments?

A: No, VAD can be given before transplant. At the Mayo Clinic, we tend to avoid VAD because of the inconvenience and complications of using an intravenous therapy (e.g. infections), as well as the fact that it is a neurotoxin. It can damage the nerves, which is important if you think you may take thalidomide in the future, Thalidomide is even a stronger neurotoxin, especially if you've had vincristine. It's not going to hurt the stem cells but it could increase the tendency for neuropathy if you're going to have thalidomide later.

Q: Is there a management for bone pain that doesn't cause nausea?

Bone pain does not always occur in myeloma but can be devastating when it does. There are new modes to treat bone pain in myeloma. Neurontin is a drug which can be used which is not a narcotic, doesn't cause nausea and vomiting and can be useful. Other patients may benefit from non-steroidal anti-inflammatories, although you have to worry about kidney failure if you take excessive amounts. Some of the pain is often due to muscle spasm, so muscle relaxants can be useful (e.g. Valium, although it is rarely used any more). Where is the pain coming from? If it's spinal pain or nerve root pain in the spine, you have the options of nerve root injections with steroids, actually killing the nerve, or vertebroplasty, where you harden the vertebrae with injections so it is no longer collapsing. There's a wide range of treatments. There's also pain clinics, where patients can see a group of doctor, including neurologists, anesthesiologists and pain specialists.

Q: What are the side effects of dexamethasone for someone with diabetes?

A: Dexamethasone is not for long-term use in myeloma. It's a good short-term drug. People with insulin-dependent diabetes may have to accept a less adequate control of their blood sugar while taking dexamethasone. They may have to monitor their glucose two or three times a day, or more. Supplemental insulin may be necessary.

Q: What is known about oral clodronate?

A: My impression is that trials have been conflicting, with no clear-cut answers. There's room for disagreement among experts as to which agent to use.

Q: Do you really have to drink 3 litres of water a day?

A: Myeloma patients should try. Some people can't drink this much or their caloric intake will go down because they always feel full. It's more important for patients with

heavy Bence Jones proteinuria. If a patient has no Bence Jones proteinuria then I allow him/her to be more lax about it. But if they have several grams of light chains in their urine, it's important to protect the kidneys. When patients with myeloma become dehydrated for any reason, such as the flu, it's important not to sit at home and wait for it to get better but to go to the hospital and get a couple of litres of fluids by IV before the kidneys suffer a dehydration effect. The main thing is to avoid dehydration.

Q: How long should treatment with melphalan and prednisone last?

A: There's room for physician judgement in this area and depends upon the response to treatment. In general, you treat until the patient reaches plateau and stays there for six months. If you stop before the protein has stopped going down, it can go back up. It's common for the protein to go up after you stop treatment. If you treat about six months into plateau and then stop, very often the plateau is maintained for about a year and a half. In general, the treatment ends up being a year to a year and a half or two years, while you're waiting for the monoclonal protein to come down and plateau. However, there's a wide range.

Q: When do you stop taking thalidomide if there is indication of progression (e.g. increase in protein or evidence of bone lesion)?

A: You have to look at several factors, such as the dose and toxic side effects the patient is experiencing. For example, if the patient is on a modest dose and not having many toxic side effects, then you can consider increasing the dose to a more effective range, or combining the thalidomide with steroids. If the thalidomide isn't working and the patient can't increase the dose because of toxic side effects, then you may need to stop and switch to another therapy.