

The Basics of Multiple Myeloma

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(Dated but still helpful in understanding Multiple Myeloma)

(THE GARDEN)

It is useful to think of the bone marrow as being a large garden. This garden contains seeds and plants and the plants bear fruit. The fruit are the mature blood cells and the seeds are the stem cells. The usual breakdown of a normal, healthy garden is approximately 60% devoted to the growth of white cells, 20% devoted to the growth of red cells and 10% devoted to the growth of platelets, the cells that clot the blood. The remaining 10% of the bone marrow is given over to a host of specialty "crops". Many have very obscure names such as basophiles, eosinophils and mast cells. The cells of interest in this discussion, however are the plasma cells, which represent 1% of the total bone marrow "acreage." Plasma cells are cells that are normally found in every adult bone marrow. They are responsible for the production of antibody proteins. There are tens of thousands of different plasma cells in a normal adult bone marrow; each devoted to the production of a different antibody protein. Most adults will have antibody proteins against prior flu vaccination, colds that they have had and polio vaccine. They will also have antibodies against minor bacterial infections as well as against wood splinters! Why the plasma cell undergoes malignant transformation and becomes myeloma cell is the subject of an enormous amount of research. Multiple Myeloma occurs in 4 adults per 100,000 per year. It accounts for 1% of all cancer and 10% of all bone marrow cancer. Other than the fact that leukemia also involves the bone marrow, there is no relationship between multiple myeloma and leukemia. This year in the United States it is anticipated that 13,700 new patients will be diagnosed with multiple myeloma. There is a higher incidence of the disease in African-Americans. When multiple myeloma develops, the 1% garden plasma cells begin to grow without control and without restraint. Therefore, the garden will become overgrown with these large numbers of unwanted plants and effectively they will function as weeds. These myeloma weeds will produce manifestations in 1 of 3 ways.

(THE WEEDS)

In the first instance, as the weeds begin to overgrow the garden, the normal production of fruit from healthy plants is impeded. Not only will you find fewer plants per acre, but also the amount of fruit produced per plant will be reduced. The upshot of this is a reduced amount of garden yield in bushels per acre. The fruit appears to be most seriously effected in multiple myeloma is the production of red blood cells. Therefore, as the weeds begin to overgrow the garden, anemia develops, resulting in the symptoms of fatigue, apathy feeling "all in", no get up and go, shortness of breath climbing stairs or up an incline, etc. In some instances, the anemia of multiple myeloma can effectively be treated with Erythropoietin (EPO, Epogen, Procrit), which in essence, is fertilizer for the healthy red blood cell plants of the bone marrow.

(BONES)

Secondly, in this garden metaphor, not only do the weeds interfere with the normal garden growth, the weeds will actually begin to invade the "casing" of the garden. Of course, the garden casing in this situation is the overlying bone and, in fact, these myeloma cells will begin to invade and destroy the overlying bone, replacing the hard calcium-rich bone with soft gelatinous colonies of plasma cells. As a result, the bone become soft and is subject to breakage underweight stress. The bones that appear to be most frequently prone to stress-induced fracture are the vertebrae and the ribs. When this develops, spontaneous rib fractures will occur, even with no trauma. Back fractures can be exceedingly painful and on x-ray often will look like simple osteoporotic (diminished bone density) compression fractures and do not necessarily demonstrate the usual findings of malignancy. These bone fractures are exceedingly painful and characteristically will produce no pain when the patient lies still. However, any attempts to flex the spine or rotate the spine such as standing from a sitting position or rolling in bed will cause excruciating pain. In addition, maneuvers that increase cavitory pressures such as coughing, sneezing or attempting to move one's bowels intensifies the pain. This type of bone destruction is one of the hallmarks of multiple myeloma and much research has been devoted to reducing these complications and currently the use of Pamidronate (Aridia) has been shown to reduce the frequency of skeletal events in patients with multiple myeloma.

(M - PROTEIN)

The third problem is that related to the protein production by the plasma cells. In most instances the plasma cells which, as one recalls, produces antibody protein does not lose this ability when it becomes a malignant myeloma cell. However, since the number of plasma cells in the bone marrow is increasing in an uncontrolled fashion, the amount of antibody protein that is produced proportionately rises. Therefore, most patients with multiple myeloma will have increased production of antibody protein and this will appear in the blood as protein spike, also referred to as the M-protein or monoclonal protein. In most patients, this M-protein does not produce any clinical symptoms; however, it is an extremely useful marker that the physician will use to infer what is going on in the bone marrow without having to put the patient through repeated bone marrow examinations to assess the extent of their disease. Since the plasma cells produce the antibody protein, rises in the antibody protein suggests an increased number of plasma cells in the bone marrow. Reduction in the antibody protein, usually as a consequence of appropriate chemotherapy administration, is inferred to reflect a reduction in the number of plasma cells in the bone marrow. In approximately 1 patient in 6, the antibody protein produced by the plasma cells will be small enough so that it will circulate in the bloodstream, filter through the kidney, and

be lost in the urine. This antibody protein lost in the urine in patients with multiple myeloma is referred to as the Bence-Jones protein. Although in most patients the Bence-Jones protein is as harmless as the blood protein is, in an occasional patient this protein can cause significant damage to the kidneys. In these instances the patient's protein can actually lead to profound kidney impairment with subsequent need for specific kidney support. In these instances the main goal of chemotherapy treatment of the multiple myeloma is to preserve kidney function and minimized the damage that results from the light chain spilling into the urine.***

(CALCIUM)

Since patients with multiple myeloma have plasma cells that are actually eroding the garden casing, this casing, which is made of calcium, is released from the bone and it enters the bloodstream. The consequence of this is elevated calcium levels in the blood, which is a concern because it can lead to mental changes, alterations in bowel function, dehydration and, if severely elevated, alterations in the heart rhythm.

(THE WEEDS KILLERS)

Given that the fundamental problem in myeloma are weeds infiltrating the garden, what then is the appropriate intervention? Clearly the correct treatment is weed killer. Weed killer and chemotherapy have many similarities to them. Of course weed killer is a cellular poison that is normally purchased in a garden store, is diluted with a garden sprayer and applied to a garden that contains weeds at a regular interval and in a careful controlled dose. Likewise, chemotherapy is a cellular poison, specifically designed to attack malignant cells, is usually diluted and has to be applied at a regular interval with careful monitoring to avoid excessive damage to the normal, healthy garden plants. Just as with weed killer, chemotherapy comes in a number of different brands or preparations. There is a high dose weed killer and then there is low dose weed killer. Among the low dose weed killers there are certain standard preparations that you all know by the name of MP or VAD (there are new chemotherapy treatments now in use***). Although there are significant differences, the basics are the same. The dose must be carefully regulated by an experienced physician to ensure that the weed killer does as much damage as possible to the weeds, without destroying the neighboring healthy garden plants. Secondly, the weed killer is applied at regular intervals varying anywhere from monthly to every six weeks. Although the weed killer is capable of producing substantial benefit in reducing the number of abnormal weeds in the garden and can produce long-term control, frequency for many years, at this point in time the weed killers that we currently have available are not capable of complete eradication of all the weeds in the garden.

(REPLANTING THE GARDEN)

Understanding the garden scenario is fundamental to understanding the rationale for stem cell transplantation. Everyone knows that chemotherapy does not just attack the bad cells but also kills the good ones as well. Weed killer, when applied to a garden that has weeds contaminating it, not only will kill the weeds but can affect the healthy garden plants. Therefore, there is a dose limitation to how much weed killer can be applied safely to a garden. If you don't give enough the weeds aren't killed. If you give too much the weeds are killed, however, the treatment; that is to restore healthy garden growth. When an individual receives weed killer, the dose is limited by the fact that if one exceeds a certain limit not only will the weeds be destroyed; the garden will be irreversibly poisoned and destroyed in its entirety. When an individual undergoes a stem cell transplant, high doses of weed killer are applied, specifically designed to destroy the garden and the weeds, however, seeds have previously been collected and frozen and then these seeds are "replanted" (the transplant which allows for the garden to regrow in a period of approximately 11 days after planting). Therefore, the transplant procedure itself does not really kill any of the weeds. However, the transplant allows us to overcome the usual limits to weed killer dosing that it previously limited that amount that could be administered. Today, massive doses of weed killer can be given in the hope that a much higher proportion of the garden weeds can be eliminated and then the previously collected seeds will regrow the garden and avoid the risks of permanent garden damage

(RISKS)

What are the risks of stem cell transplant? Everyone recognizes that when one poisons a weed-ridden garden with a high dose of weed killer, the garden is rendered barren. When seeds are planted in a garden and given appropriate amounts of water, light and fertilizer, the seeds will not turn into full growing plants bearing fruit in 1 or 2 days. Using tomatoes as an example, this entire process takes nearly 3 months and the quality of the soil or the amount of fertilizer administered cannot change this. The duration of time between tomato seeds and tomatoes is dictated by the germination time of tomatoes and this is a process that cannot be sped up. Likewise, bone marrow stem cells have a "germination time". In most instances it takes approximately 11 days, there is very little garden activity and most of the normal functions of the bone marrow have to be supported by the transplant team. The deficiency of red blood cell output from the garden can be accommodated by transfusions of blood. Likewise, the deficiency of platelets which clot the blood can also be replaced by transfusion. However, white cells cannot easily be transfused. Therefore, the function of white cells, which is to protect the body against infection, must be temporarily substituted by the use of multiple antibiotics. Even though these antibiotics are highly effective in preventing infection, they are not a substitute for having one's own white cells. Therefore, the major complication of stem cell transplant is infection that occurs due to a reduction of the white blood cell plants from the high dose weed killer. The total duration of a low white blood cell count is usually between day +4 and day +11 following the transplant and infection accounts for the major risk associated with the procedure. Nonetheless, in an experienced center, the use of high dose weed killer with the seed replanting (stem cell transplant) can result in a relatively low risk of in-hospital complications.

(And, with today's new treatments, your garden may remain "weed free" and without the use of "weed killers" for many years to come!)