

Introduction

Multiple myeloma (MM) is a B-cell lymphocyte malignancy classified by the overabundance of plasma cells forming tumors in the bone marrow. The disease is exceedingly progressive and quickly reproduces to induce anemia, hypocalcaemia and attenuation of bone density. Tumors are detected by the presence of paraprotein in the body and are formed by immunoglobulin gene rearrangement and lack of cell evolution due to somatic hypermutation (1). The bone marrow environment associated with MM can augment tumor growth and migration, and additionally can lead to the development of drug resistance. Tumor growth is caused by adhesion molecules on MM cells binding to extracellular matrix proteins and bone marrow stromal cells, thus triggering cytokine-mediated cell growth (1). Studies over time have developed a number of treatment options available to treat MM including chemotherapy, radiation, prescription drugs and multiple types of haematopoietic stem cell transplantations. However, MM remains highly incurable regardless of high-dose chemical and biologically based treatments. Recent studies have begun to focus on the interaction between myeloma cells and their bone marrow microenvironment in order to reduce development of the disease generated by the human body. A new area of study looks into the use of thalidomide, an immunomodulatory drug which stimulates T-cell promulgation and production of interleukin. Additionally, the greatest benefit of thalidomide lies in its ability to modulate cell adhesion and reduce interaction between myeloma cells and bone marrow cells. Currently appropriate dosages of thalidomide are uncertain, especially with regards to increased side effects. The combination of thalidomide with chemotherapy has proven

to have the highest risk of side effects specifically with venous thromboembolism (VTE) the blockage of arteries in the lungs. Future research should concentrate on these areas of study in order use thalidomide to its fullest potential as well as to increase the rate of survival for MM patients.

Background of Multiple Myeloma Research

Presently, there are many treatment options available for MM patients, including chemotherapy, radiation, prescription drugs and several types of haematopoietic stem cell transplants. Currently, stem cell transplantation is the most common treatment in conjunction with chemotherapy and other high dose drugs such as melphalan. The use of melphalan treatment for multiple myeloma was attempted in the 1980s in order to instigate haematological remissions and extend patient survival; however, the mortality rate was high without the aid of stem-cell support. Therefore autologous, allogeneic, and syngeneic transplantation were developed to provide support for the treatment. In the most conventional transplant, autologous transplantation, leukapheresis is used to collect peripheral stem cells from the patient's body after a short treatment with cytotoxic drugs. High-dose treatment must be given 4-6 months prior to the beginning of the transplant. Before any type of transplantation can occur, only a very small percentage of MM cells can be present in the body. Patients are treated with chemotherapy before transplantation in order to kill the majority of MM cells. The leftover stem cells (CD34-positive cells), treated with cytotoxic drugs but still contaminated with myeloma cells, are incubated with a biotinulated antibody and are passed through a column of avidine-coated

polyacrylamide beads. The beads attract the CD34-positive cells containing the antibody and are later removed using a magnet. Cells without the antibody are put back into the patient's body (2). Systemic and allogeneic transplantations, although not as common have also been used for support to accompany melphalan treatment. The option of transplantation is often times successful for remission of MM; however, no cure has been reported. New biologically based treatments have also been discovered which will eventually reduce the number of patients treated with transplants.

Cytokine inhibitory and immunomodulatory drugs are inhibitors that have been determined to have a successful effect on significantly reducing the tumor necrosis factor α production in myeloma cells. Thalidomide is a immunomodulatory drug treatment which can restrain the advancement of myeloma cells by DNA oxidative damage and inducing apoptosis to myeloma cells regardless to whether they are drug resistant. Furthermore, thalidomide is capable of moderating cell adhesion and may be able to interfere with stimulatory interactions between myeloma cells and bone marrow cells, and increasing the growth of T-cells and natural killer cells (3). However, the ideal dosage of thalidomide has yet to be determined. Many doctors have conducted research to establish the most effective amount of thalidomide but these results have varied among experiments. Some researchers have found that patients who are given more than 42 g of thalidomide within the first three months of their diagnosis have better response rates. In contrast, other doctors have received positive results using thalidomide amounts ranging from 50 to 200 milligrams per dosage (mg/d). The minimum dosage required for patient response has been around 200 mg/d in all experiments. When quantities were augmented to 800 mg/d severe skin rash became evident. A precise amount of thalidomide needs to

be uncovered in order to stimulate a positive response without the obstruction of side effects.

Thalidomide has been given as an unaccompanied treatment with a response rate of 36% and an average response duration greater than one year. In studies done using thalidomide as a solo treatment, 30-45% of patients with relapsed or refractory disease achieved a partial response thereby confirming the activity of thalidomide as a single agent in advanced myeloma. Thalidomide has also been tested with various types of chemotherapy including dexamethasone, cyclophosphamide, etoposide, doxorubicin and cisplatin. However, an increased risk of venous thromboembolism is seen when thalidomide is used in conjunction with chemotherapy especially for patients with newly diagnosed myeloma. When the tumor is at its maximum density the combination of chemotherapy and thalidomide with this high level of tumor growth, causes prothrombic problems such as VTE. Patients with MM can also suffer multiple complications including immobility, dehydration, increased plasma viscosity and recurring infection. Other typical side effects associated with the use of thalidomide include peripheral neuropathy, sedation, and constipation, birth defects in pregnant women, bradycardia, rash, and hypothyroidism. Even though the outline of side effects of thalidomide is high, they are readily tolerated by the majority of patients (3). However, researchers need to study how to reduce side effects of thalidomide, especially those in conjunction with VTE.

Future Treatment Prospects

Thalidomide has proven to show substantial results when used as a single agent or in conjunction with other therapies. However, the ideal dosage is still uncertain as well as its combination with chemotherapy (3). Researchers need to determine appropriate dosages of thalidomide needed to treat MM without increasing the risks of side effects yet still being able to control and treat myeloma cells effectively. Regulating thalidomide dosages will aid in maintaining consistency in treatment and will help us determine if we can give too much of the drug resulting in an increased risk of VTE that will outweigh the benefit of the drugs' effects on myeloma cells. Furthermore, we need to establish the minimum amount of thalidomide that can be given to a patient and still be effective. Thalidomide as a means of treatment is very beneficial because it works to seclude myeloma cells from their bone marrow environment. Once secluded, doctors can target only the contaminated cells for treatment as well as prevent future growth and spread of the disease. Determining the optimal amount of thalidomide will allow doctors to use the drug to its fullest capability without coping with increased risk of detrimental side effects.

In addition, researchers need to investigate why the combination of thalidomide with chemotherapy carries a considerably higher risk of VTE and why this side effect is more prevalent in newly diagnosed patients. Thalidomide has proven to be very successful in assimilation with various types of chemotherapy. However, because researchers have hypothesized that the combination of chemotherapy, thalidomide and large tumor masses result in a larger risk of VTE, we should focus on treating patients

with greater amounts of chemotherapy in order to reduce tumor size then gradually decrease amounts of chemotherapy and simultaneously increase thalidomide levels. Hopefully, with the reduction of tumor size and the eventual decrease in chemotherapy levels, the possibility of VTE will decrease as well. We should also study the need for additional medications in order to prevent VTE if the disease becomes evident.

With these recommendations of how to further study multiple myeloma, side effects and treatment options doctors should be able to increase the rate of positive response from MM patients without destructive side effects. Experimentation and tests will perhaps lead to increased remission percentages among patients and ultimately lead to a cure for multiple myeloma.

Pledge