LITERATURE REVIEW

# INTRODUCTION:

A literature review is a “*critical analysis of a segment of a published body of knowledge through summary, classification, and comparison of prior research studies, reviews of literature, and theoretical articles*” (University of Wisconsin Writing Center).

According to Cooper (1988), "*a literature review uses as its database reports of primary or original scholarship, and does not report new primary scholarship itself. The primary reports used in the literature may be verbal, but in the vast majority of cases reports are written documents. The types of scholarship may be empirical, theoretical, critical/analytic, or methodological in nature. Second a literature review seeks to describe, summarizes, evaluate, clarify and/or integrate the content of primary reports*."

Purpose of this detailed literature review is to highlight and compare different treatment guidelines available for the hematological cancer MULTIPLE MYELOMA in terms of their clinical and cost effectiveness.

Multiple myeloma is considered as a *“plasma cell malignancy resulting in high levels of monoclonal immunoglobulin in serum and of free light chains (Bence–Jones protein) in urine.”* (Roitt Glossary, 2011). According to another definition, “*a malignancy of plasma cells (a form of lymphocyte) that typically involves multiple sites within the bone morrow and secretes all or part of a monoclonal antibody*” (Definition of Multiple Myeloma, 2011)

Finally, the study will conclude the potential strengths and loopholes in existing treatment guidelines. A thorough study of will lead to a concrete basis for the development of further improved and both cost and clinical efficient treatments in the favor of mankind.

# THE STUDIES:

## Background

Several authors conducted various studies to assess the efficiency of bisphosphonates on myeloma related bone destructions. High rate of morbidity and mortality in multiple myeloma is related to progressive bone destruction. Patient may survive for many years post-diagnosis, so clinicians attempted to devise therapeutic procedures to improve quality of life. Initially researchers used fluoride for this purpose. Later, some researchers tried calcium and fluoride in combination. But latter approach was not effective. Calcium and fluoride combination proved detrimental to patient’s health because of its side effects. Latest approach in treatment of myeloma induced bone disease is the use of bisphosphonates. These agents induce osteoclastic apoptosis which finally results in the inhibition of osteoclastic bone resorbtion. New generations of bisphosphonates have been introduced, and these drugs are very effective in relieving bone pain. They also decrease urinary excretion of calcium and hydroxylproline thus indicating decrease bone turnover. This phenomenon was first shown with pamidronate (Van Breuklen et al, 1979), and then with clodronate (Siris et al, 1980). Second generation (Pamidronate; Aredia) and third generation (Zoledronic acid; Zometa) bisphosphonates were also introduced to improve efficiency of bisphosphonates.

FDA in the United States have approved pamidronate and zoledronic acid for myeloma patients with bone disease with or without hypercalcemia. Basis of these approvals were those studies which evaluate safety and efficacy in myeloma patients and concluded satisfactory results in bone pain, reduced need for radiation therapy, and reduction in vertebral and non-vertebral fractures (Berenson et al, 1995).

Medical Research Council in the United Kingdom conducted a study in which clodronate was the bisphosphonate used (McCloskey et al, 1998). Along with this, several other studies conducted in Europe are consistent with the above findings. Latest approval of the zoledronic acid third generation bisphosphonate for use in bone disease was based on the findings of studies which showed a marked reduction in skeletal-related events in myeloma patients (Berenson et al, 2001, Rosen et al, 2001). This agent is more potent than pamidronate, and can be used by infusion over a shorter period of time (but not less than 15 minutes).

LIMITATIONS:

Bisphosphonates have been demonstrated very effective in treatment of myeloma patients. But still this area needs further research. Several limitations are associated with its use.

* Alendroante is a compound about which there is no information regarding its clinical effectiveness, its doses and timing of administration.
* The newer bisphosphonate ibandronate is not much effective in clinical studies because of its doses which used in studies were not optimal (Menssen et al, 2002).
* Bisphosphonates are claimed to be cytotoxic or cytostatic to tumor cells according to in vitro studies (Shipman et al, 1998), but there has been little or no beneficial effects of these drugs on tumor burden in patients or in experimental animal models of myeloma.
* Other issues that leads to doubt on the successful use of bisphosphonates includes whether an efficacious orally available bisphosphonate can be developed, whether bisphosphonates can be given to those patients who are in the early course of the disease and whether we can use it as a preventive method in patients before they have obvious bone disease or with MGUS
* Most important requirement is to evaluate the effects of these drug on survival of the patient.

Above limitations indicates need of further research in this area, to introduce new and safe bisphosphonates or other related drugs. These drugs are expected to have positive effects on patient’s survival and are convenient because of their easy mode of administration (oral).

## Dr. Pozzi - ASH 2008

In this study, author used mainly DKK-1 neutralizing antibody for the treatment of MULTIPLE MYELOMA related bone diseases. Basis of this study was to concentrate on osteoblastic activities of bone and promote osteobalstogenesis by using DKK-1 antibody. This antibody is an inhibitor of the wingless int(wnt) pathway, which is considered to be very important in osteoblastogenesis. The aim of this study was to test the effect of a Dkk-1 neutralizing chimeric antibody (Mab B3) on osteoblasts (OB), osteoclasts (OC) and MM (multiple myeloma) cells in the bone microenvironment. First, the author tested the expression of Dkk1 in plasma and bone marrow of 16 MM patients and 10 MM cell lines. Dkk1 levels were >18 ng/mL in 2 out of 16 patients; levels were comparable in blood and bone marrow plasma. In contrast, very little Dkk1 (2-9 ng/ml) was produced by bone marrow stromal cells (BMSC). One out of 10 MM cell lines (INA-6) expressed low concentrations of Dkk1 in the supernatant. After that, author tested the effect of Mab B3 on MM cell lines, in the presence or absence of BMSC, and on OB and OC from MM patient derived bone marrow. The effects on OC were evaluated by TRAP staining and pit formation. Effects on OB were assayed by alkaline phosphatase staining and alizarin red assays for calcium deposition. Results of this study summarized that Mab B3 antibody did not demonstrate direct cytotoxic effects on MM cell lines, but increased differentiation and calcium deposition in OB. This increment is dose dependent. Mab B3 antibodies inhibited OC differentiation and function. These results indicate Mab B3 has anabolic bone effects and can be used for the treatment of MM related bone diseases.

LIMITATIONS:

Shortcoming of this study includes effects of Mab B3 on MM cell lines. This antibody does not show any kind of cytotoxic effects on MM cells. Ongoing studies are addressing the effect of Mab B3 on MM cells in the context of OC and OB. Mab B3 is also undergoing in vivo testing in a SCID-hu model. This model is bearing INA-6 MM cells.

Future studies are required to evaluate Mab B3 effect in combination with catabolic agents such as bisphosphonates. Aim of these studies is to restore normal bone homeostatsis.

## William Bensinger, MD

According to the author, transplants can prove to be a revolutionary treatment in MM patients. Transplants can be autogenic or allogenic. When bone marrow or peripheral blood stem cells of the patient itself are used then it is known as autogenic transplant. However, if a donor is used for the same purpose then it is called allogenic transplant.

In case of allogenic transplantation a very high dose of chemotherapeutic drugs is used. Drugs mainly used for this purpose are: fludarabine, cyclophosphamide or melphalan. The drugs cyclosporine, methotrexate, anti-thymocyte globulin and mycophenolic acid are usually added to provide additional immunosuppression. This can be with or without radiation which is usually given to the entire body at once (total body irradiation). Low dose of radiation (200cGy) should be used for this purpose. Main purpose of radiations are:

* cytoreduction- means effective killing of the myeloma cells
* immunosuppression- means sufficient reduction in the patients’ immune system so that donor graft can be established and prevent rejection

Allogenic transplants induce graft versus myeloma effect. It means donor graft is capable of seeking out and destroying myeloma cells in the patient. These transplants are also known as NON-ABLATIVE or MINITRANSPLANTS.

Author conducted a study in the favor of fact that “graft versus myeloma” effect works best in the minimal disease condition at Fred Hutchinson Cancer Research Center. The preliminary results of this study suggest that donor engraftment can be established safely with a relatively low mortality rate of 10%. For patients with advanced multiple myeloma or who have relapsed after an autologous transplant, significant responses appear only after patient recieves salvage chemotherapy prior to the "mini-transplant". This has been confirmed by several other transplant centers.

Further in this study "tandem" autologous/mini-allogeneic transplant approach is used. In this approach, patients first have their stem cells harvested using chemotherapy and G-CSF and then they undergo an autologous transplant. This transplant is done under high dose of melphalan which kills myeloma cells. Patients are then allowed to recover from the autologous transplant for 2-3 months. The final step in this study was to perform the mini-transplant. Author omitted the fludarabine from the mini-transplant regimen in the tandem approach because there was sufficient immunosuppression provided by the autologous transplant. Preliminary results suggest that this strategy is well tolerated with a 15% risk of death, reliable engraftment and a 50-60% of obtaining a complete remission in which all evidence of myeloma is gone. Further follow-up is needed to check durability of these remissions.

According to author, it is not yet possible to definitely say that mini-allografts are safer than standard allografts. Most of studies have utilized matched family members as donors. Fewer trials have concluded that use of matched unrelated donors ("MUDs") appear to be associated with a higher risk of graft rejection and graft-versus-host disease.

LIMITATIONS:

* Transplants have to be used with high dose regimens. Due to this side effects of drugs are likely to appear. As a result, complications and even death result from these types of transplants. Patients that are older or have pre-existing organ damage are at an even greater risk of complications and death.
* Drugs used under this kind of transplantation do not provide enough tumor killing, so further need of other chemotherapeutic agents is mandatory.
* These transplants rely mainly on the graft-versus-myeloma effects and work best when a person's cancer grows slowly so the newly engrafted stem cells have sufficient time to grow and mount an immune attack. But it is not always possible that cancer cells will grow slowly.

## Robert A. Kyle, MD

According to the author, if the patient is less than 70 years old, autologous peripheral blood SCT is considerable. The stem cells must be collected before the patient is exposed to alkylating agents. Mortality rate with autologous SCT is only 1% to 2%. Transplantation can be started as soon as the patient has recovered from stem cell collection but it can be delayed following collection, when patient is treated with alkylating agents and delay the transplant until progressive disease develops. In both methods survival is same but patients given early transplants are spared from the inconvenience and cost of chemotherapy. Autologous SCT is applicable for up to 50% of patients with MM.

LIMITATIONS

Major shortcomings of autologous SCT are that myeloma is not eradicated even with large doses of chemotherapy, total body irradiation (TBI), or both and that autologous peripheral stem cells are contaminated by myeloma cells or their precursors

## Dr. Mario Boccadoro

Dr. Mario Boccadoro and colleagues of the University of Torino conducted a study using intermediate doses of melphalan. They conducted a study using intermediate doses of melphalan. They treated 71 MM patients with two or three courses of melphalan 100 mg/m2 (MEL100), followed by stem cell support. Patients’ median age was 64 years. These patients were matched on the basis of age and beta2-microglobulin (b2-MG) levels with those patients who were being treated with oral melphalan and prednisone (MP). Complete remission (CR) occurred in 47% of the MEL100 and 5% of the MP patients. Median event free survival (EFS) was 34 months in the MEL100 group and 17.7 months in the MP group (P <0.001). Median overall survival(OS) was 56+ months for MEL100 and 48 months for MP (P<0.01). In a multivariate analysis, superior EFS and OS were observed in patients presenting with low b2-MGlevels at diagnosis and in patients receiving MEL100. In a second analysis, Dr. Boccodoro compared the effect of MEL100 with standard MP in patients. Median age of these patients was 67 years. Thirty-one patients aged 65 to 77 years were treated with two or three courses of MEL100 and compared with a group of 31 patients treated with MP. Matching was done on the basis of their stage at diagnosis and their serum b2-MGlevels. The EFS (P<0.005) and OS (P<0.01) were superior for the MEL100 patients than those patients who were receiving MP.

This study concluded that MEL100 appeared to be superior to standard MP in both the general population and in patients more than 65 years of age.

Next investigation in this study was concentrated on MEL100 versus MEL200. Investigators compared 81 patients treated with MEL100 with 81 patients receiving MEL200 matched for b2-MG and stage. All patients were treated with single (n=45) or double (n=36) autologous transplantation. Mortality rate was 4% with MEL100 and 7% with MEL200 patients. The CR rate was 43% with MEL100 and 63% with MEL200. EFS was 30 months in the MEL100 group and 33 months in the MEL200 group. OS was 57 months for MEL100 and 53 months for MEL200.

Conclusion of this study was that MEL100 was similar to MEL200 from the standpoint of CR, EFS, and OS despite a significant patient age difference (63 vs. 50 years) (P<0.0001 CR rate improved by 20% with MEL200, but this was not enough to produce a significant outcome improvement. These are non randomized trials, so conclusions should be made cautiously.