PREDICTIVE EFFECTS OF MALNUTRITION INDICATORS FOR MORBIDITY AND MORTALITY AMONG BLOOD AND MARROW TRANSPLANTATION RECIPIENTS: A RETROSPECTIVE CHART REVIEW

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BY

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To the Dean of the Graduate School:

I am submitting herewith a dissertation written by Srisuda Lecagoonporn entitled "Predictive Effects of Malnutrition Indicators for Morbidity and Mortality among Blood and Marrow Transplantation Recipients: A Retrospective Chart Review." I have examined this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Nursing Science.

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DEDICATION

To the memory of my father,

who inspired me in

education and perseverance.

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ABSTRACT

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PREDICTIVE EFFECTS OF MALNUTRITION INDICATORS FOR MORBIDITY AND MORTALITY AMONG BLOODAND MARROW TRANSPLANTATION RECIPIENTS: A RETROSPECTIVE CHART REVIEW

AUGUST 2010

The purpose of this study was to identify complications related to the blood and marrow transplantation (BMT) process, the presence of malnutrition among patients who received myeloablative allogeneic BMT, and the predictive effects of malnutrition indicators to the outcomes of BMT. Six research questions related to malnutrition were investigated: (a) weight and albumin recovery patterns; (b) malnutrition indicators and outcomes of BMT; (c) body mass index (BMI) and incidences of transplant related mortality; (d) degree of mucositis and its relationship to transplant related infections; (e) predictive ability of BMI and serum albumin levels and infection incidences; and (f) predictive ability of BMI and serum albumin levels and mortality incidences during the first year post BMT.

The conceptual framework chosen for this study is based on the pathways of cancer aggression (1977) which demonstrate how cancer interferes with multiple organs and function leading to host depletion, morbidity, and mortality. This study is a retrospective chart review from 110 electronic medical records of patients diagnosed with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS), who received

the same regimen of myeloablative, allogeneic BMT from one cancer institution during August 2005 to June 2008.

Findings revealed that there was no conclusive agreement among three raters identifying the patterns of weight recovery and of serum albumin levels among 110 post-allogeneic BMT recipients during the 100 days post-BMT. There were subjects who experienced weight loss (68%) and had hypoalbuminemia (97.3%), indicating malnutrition after BMT. Weight loss was not related to transplant mortality but it significantly contributed to an increase in transplant related infections. Hypoalbuminemia was significantly related to both transplant related mortality and infection especially when serum albumin dropped below 3 gm/dL. The body mass index was not related to transplant related mortality during 100 days post BMT. Although the majority of subjects experienced mucositis to the point that it interfered their eating and swallowing solid food, severity in mucositis did not contribute to transplant related infection. Both BMI and hypoalbuminemia were significant predictors to transplant related infection during 100 days post BMT. Predictors for transplant related mortality in one year have not been identified.

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CHAPTER I

INTRODUCTION

In 2009, approximately a total of 1,479,350 new cancer cases were diagnosed and 562,340 Americans died of cancer. One in four deaths in U.S. is due to cancer. Cancer accounts for more deaths than heart disease in person younger than 85 years of age (Jemal, Siegel, Ward, Hao, & Xu, 2009). Surgery, radiation therapy, and chemotherapy remain the standard treatments for cancer. However, newer treatments such as biologic response modifiers and blood and marrow transplantation (BMT) have evolved from an experimental to accepted therapies for several cancer types. Bone marrow transplants have been particularly effective at treating cancers of the blood such as leukemia. In 2006, there were at least 18,560 BMT procedures performed in North America (Pasquini & Wang, 2009). Although BMT holds an active promise of a cure for acute leukemias, patients have a long, stressful, and expensive course of recovery and are subject to life threatening complications.

The major complications after BMT are related to prolonged impaired immunological function and patients are prone to various degrees of gastrointestinal failure (Murray & Pindoria, 2009). One of these complications is a poor nutritional status. An adequate nutritional status is difficult for many BMT patients to maintain. Pre-BMT patients are subjected to high dose chemotherapy and/or radiation which frequently leads to side effects such as mouth sores, nausea and vomiting diarrhea, and loss of appetite.

Post BMT recipients consume a highly restricted diet for at least 3 months post transplant or until all immunosuppressive therapy has been stopped. Raw and undercooked products (meat, eggs, vegetable sprouts, fruits); unpasteurized products (milk, cheese, yogurt, beer commercial fruit and vegetable juices); refrigerated salsa products; unroasted nuts; raw or non-heat-treated honey, and all miso products are prohibited (Lipkin, Lenssen, & Dickson, 2005). This type of diet limits food choices and palatability which has an effect on BMT recipients' nutritional status and often leads to malnutrition.

Malnourished patients often experience more difficulties in successful recovery from BMT process. Underweight patients had a higher incidence of infectious complications, poor survival time (Le Blanc, Ringden, & Remberger, 2003), and higher non-relapse mortality rate during the early period post transplantation when compared to normal or over weight patients (Deeg, Seidel, Bruemmer, Pepe, & Appelbaum, 1995; Le Blanc et al., 2003). Recognition of the early signs of malnutrition is the key to prevent severe malnutrition and increase the success of cancer treatment.

Problem Statement

The purposes of this study were to: (a) identify primary indicators that reflect the presence of malnutrition; and (b) evaluate the predictive effects of these indicators on morbidity and mortality among post BMT recipients.

Rationale for the Study

Blood and marrow transplantation is a complex and aggressive therapy. Post-BMT complications involve multi-organ dysfunction related to: (1) the conditioning regimen; (2) prolonged impaired marrow function; and (3) donor-recipient

histocompatibility. These interrelated complications alter metabolic function and nutritional status by placing patients at increased risk for morbidity and mortality during the post-transplant recovery period (Herrmann & Petruska, 1993). Numerous prescribed medications for infection prophylaxis and immunosuppressive therapy have side effects causing gastrointestinal discomfort, electrolyte imbalance, and organ dysfunction (Poliquin, 1997). Treatment for one complication may cause exacerbation of another complication (Champlin & Gale, 1984).

Nutritional intake deficit and eating problems are considered the most important quality of life issue (physical well-being and symptoms domain) among BMT recipients and their caregivers (Ferrell et al., 1992; McGrath, 2002). Malnutrition results in both increasing muscle fatigue and alteration of muscle contraction and relaxation (Lopez, Russell, Whitwell, & Jeejeebhoy, 1982). Muscle weakness affects an individual's physical function to carry out activities of daily living such as meal preparation (Whitman, 2000), eating, and self-grooming. The progressive ill appearance related to the malnourished condition may contribute to more social isolation and depression (Ottery, 1995).

Malnutrition remains a largely unrecognized problem in healthcare settings. Physicians often fail to recognize undernourishment patients. A case-scenario-based questionnaire study was conducted among 357 specialist oncological trainees who cared for patients with the highest prevalence of malnutrition. Majority of these oncologists (80%) expressed uncertainty or lack of confidences in their ability to identify malnutrition. They reported three principal barriers to initiate nutritional intervention: (a)

lack of clear guideline ($n = 231$, 69%); (b) lack of knowledge ($n = 201$, 60%); and (c) lack of time ($n = 188$, 56%) (Spiro, Baldwin, Patterson, Thomas, & Andreyev, 2006).

There is no single nutritional assessment tool that adequately characterizes nutritional status. The most important part of developing a comprehensive nutritional profile is the primary indicator that can reflect the presence of malnutrition and draw attention from clinicians. The second step is finding objective indicators that assess the severity and confirm the malnutrition condition. Finally, malnutrition is best managed by periodic nutritional measurements that evaluate the effectiveness of nutritional therapy (Blackburn, Bistrain, Maini, Schlamm, & Smith, 1977).

The toxic nature of BMT has deleterious effects on patients' ability to maintain an optimal nutritional state (Layton, Gallucci, & Aker, 1981). Bone marrow transplant patients have numerous factors – both pre-operative and post-operative that contribute to potential malnutrition. Subsequently, malnutrition contributes to morbidity and mortality. Early detection through nutritional assessment has the potential to circumvent or diminish these occurrences during the immediate post-transplant period. This study will examine the nutritional status of post BMT patients to identify significant indicators of malnutrition in order to develop nutritional interventions that have the potential to improve clinical outcomes for post BMT patients.

Conceptual Framework

The conceptual framework chosen for this study is based on pathways of cancer aggression (Costa, 1977). Costa developed this pathway from a literature review in order to facilitate clinician recognition of an inadequate nutritional stage among patient with cancer. He proposed that this substantial morbid condition was potentially revisable by means of hyperalimentation.

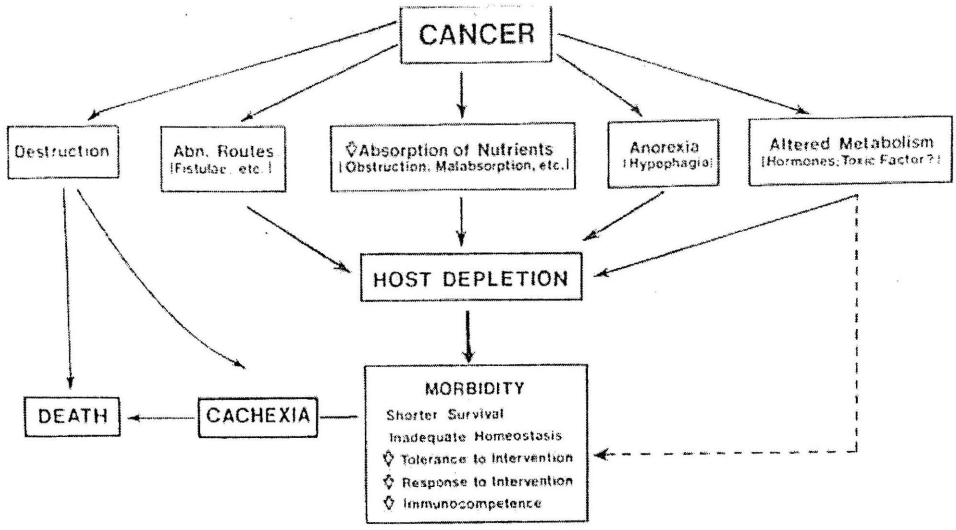

Figure 1. Pathways of cancer aggression
Note:Reprinted with permission from "Cachexia, the metabolic component of neoplastic disease" by G. Costa, 1977, *Cancer Research, 37*(7, part 2), 2327-2335.

Cancer, a growth of malignant cells in the host, is associated with manifold effects on organs and functions, with multiple interactions between destruction, attempted repair, and homeostasis. There are two basic mechanisms which influence the devastation of malignant cancer in hosts: local and systemic effects. The local effect, space occupation of tumor growth within the tissue of vital organs such as brain, heart, or lungs

leads to profound alterations of essential physiological functions (Costa & Weathers, 1964). Another localized effect is abnormal drainage from fistulas related to tumor growth in the alimentary canal that contributes to bleeding and loss of essential nutrients - a cause of host depletion (Shils, 1977).

Cancer can intoxicate the host with the production of distant substances that act systematically known as paraneoplastic syndromes (Hall, 1974) or systemic effects of tumors (Costa & Holland, 1965). There are a triad of host responses: (1) anorexia with diminished of food intake; (2) wasting of body tissue, predominantly muscle and fat and (3) hypermetabolism for the nutritional state of the host; (Costa, 1963; Waterhouse, 1963).

Anorexia, a loss of appetite, or a decrease in the spontaneous consumption of food, is a common phenomenon in most patients with cancer at some time during their illnesses. The pathogenesis of anorexia is unclear with multiple possible causes: (a) nonspecific manifestation of diseases; (b) alterations of taste and/or smell perception; (c) production of lactate, ketones, or other unknown tumor toxins; (d) direct effect of tumor on appetite center in the brain (Costa, 1977); and (e) psychological factors (devastation by the thought of impending death from cancer) (Holland, Rowland, & Plumb, 1977).

The tumor has the ability to parasitize the host by competing for nutrients which should be partitioned to the host's requirements. The growth of tumor is independent from the host's regulatory mechanisms and leading to host depletions of fat, carbohydrates, and protein (Costa, 1977). Weight loss, the loss of biomass, occurs as a consequence of anorexia or a warning sign of cancer (Shils, 1977).

Profound alterations of host lipid metabolism can be related to lower food consumption from anorexia or increased energy expenditures from active malignant neoplastic disease. A high rate of glyconeogenesis from lactate contributes to energy loss and fat depletion of the host. The loss of structural lipids, in severe cases, occurs with irreversible consequences for cell functions and eventually morbidity of the host (Costa, 1977).

The overall result of the systemic effects of tumors is malnutrition, or cachexia. Cachexia is a syndrome characterized by weakness, anorexia, depletion of host components, electrolytes and water abnormalities, and progressive fading of vital functions (Costa, 1963). The pathology of protein malnutrition secondary to poor nutrition contribute significantly to overall morbidity among cancer patients related to inability to tolerate cancer treatments, with shorter survival time, and higher risk of infections (Copeland, Daly, & Dudrick, 1977).

This conceptual framework reflects multiple risk factors related to malnutrition among BMT recipients. Post transplant complications involve both psychological distress and physical limitations that lead to lower oral food consumption. Side effects from multiple prophylaxis medications usage contribute to abnormal metabolism of fat, carbohydrate, and protein among BMT recipients.

Blood and marrow transplantation offer hematologic malignancy patients a second chance of survival. The complex medical aspects of transplantation: high-dose chemotherapy, total-body irradiation, changes in physical appearance, long-term isolation, and limited visitations including physical contact with others are related to

emotional distress among BMT recipients. The greatest period of emotional distress and vulnerability are the time after admission to the hospital for transplantation and before infusion of donor's bone marrow (Fife et al., 2000). Fear of uncertainty, anxiety, grief, and depression can diminish appetite and food intake.

Gastro-intestinal side effects related to pre-conditioning regimens may interfere with adequate oral intake among post BMT transplant recipients. Iestra et al. (2002) found that 66 of 100 (66%) stem cell transplantation recipients experienced eating difficulties during the first 50 days post transplantation. Nutrition-related side effects among these 100 recipients were: poor appetite more than 2 days (65%); alteration of taste (61%); dry mouth (56%); and nausea more than 2 days (37%).

Weight loss during 3 to 12 months after allogeneic transplantation had been reported 54 of 192 (28%) marrow transplant recipients (Lenssen et al., 1990). Oral mucositis was the single most debilitating side effects influenced eating difficulties among 16 of 38 (42%) post BMT recipients (Bellm, Epstein, Rose-Ped, Martin, & Fuchs, 2000). Therefore, post- allogeneic BMT recipients are at risk for malnutrition.

Increased energy expenditures, hypermetabolism were observed among 21 of 24 (88%) patients during 2-14 days post BMT and prior to the development of major complications (Annis, Henslee-Downey, DeWitt, & McClain, 1991). Resting metabolic expenditure among allogeneic marrow transplantation was generally increased 79% to 121% of basal energy expenditure during 3 weeks from chemo-radiotherapy, pre-condition period (Hutchinson, Clemans, Springmeyer, & Flournoy, 1984). Szeluga et al. (1985) suggested that energy requirements during the first 30 days post BMT should be

considered higher among children, males, and patients with acute graft-versus-host disease.

Graft-versus-host disease (GVHD) is a major complication associated with a donor-anti-recipients reaction mediated by donor T-cells against disparate histocompatibility antigens on recipient tissue. The primary target organs in GVHD are skin, liver, and gastrointestinal tract (Gale, 1985). This complication occurred among 121 of 192 (63%) patients post BMT (Lenssen et al., 1990). Cyclosporin therapy for GVHD prophylaxis has been associated with alterations in lipid metabolism (Nemunattis, Deeg, & Yee, 1986). Elevated serum triglyceride concentration was observed among 22 of 38 (58%) patients undergoing allogeneic BMT (Carreras et al., 1989).

Steroids therapy given as GVHD prophylaxis among BMT recipients have profound effects on impaired glucose tolerance and induced hyperglycemia. Total body irradiation, and myeloablative therapy using cyclophosphamide in combination with busulfan cause direct damage to pancreatic beta cells function. Smedmyr, Wibell, Simonsson, and Oberg (1990) found that all 13 (100%) patients in their study who received either autologous or allogeneic BMT experienced impaired glucose tolerance during 6 months after transplantation.

Assumptions

The following study assumptions were derived from the Conceptual Framework (Costa, 1977):

1. The consequences of impaired food intake or food absorption are a major contributor to the overall morbidity of patients with cancer.
2. Cachexia syndromes are potentially reversible conditions if they are detected and intervened at early stage.

Research Questions

Six research questions were tested in this study:

1. What are the patterns of weight recovery and serum albumin levels among post-allogeneic BMT recipients during the 100 days post-BMT?
2. What are the relationships of transplant related infections and transplant related mortality associated with weight loss and hypoalbuminemia as indicators for malnutrition among post-allogeneic BMT recipients during the 100 days post-BMT?
3. Do allogeneic BMT recipients with a low body mass index (underweight or normal weight) prior to BMT have a higher incidence of transplantation-related mortality rate than allogeneic BMT recipients with high body mass index (overweight or obese) during the 100 days post-BMT?
4. Do allogeneic BMT recipients with mucositis grade III and IV have a higher cumulative incidence of transplantation-related infections than recipients with mucositis grade I and II during the 100 days post-BMT?

5. Are the malnutrition indicators of lowest BMI and the lowest serum albumin levels during the first 30 days post BMT predictive of infection during first 100 days post BMT when controlling for the variables age of recipient, time of transplant, and development of acute GVHD or relapse in 100 days?
6. Are the malnutrition indicators of the lowest BMI, and the lowest serum albumin levels during the first 30 days post BMT predictive of mortality during one year post BMT when controlling for the variables age of recipients, time of transplant, and development of chronic GVHD or relapse in one year?

Definition of Terms

The following terms were defined for the purposes of this study:

1. Post-allogeneic blood and marrow transplant recipient is conceptually defined as a person who received his/her blood and marrow transplantation from a donor with a matching human leukocyte antigen (HLA) (Santos, 1984). The operational definition for this study is a person, 18 years or older with a diagnosis of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), receives the first allogeneic BMT from a related or unrelated donor in a large medical cancer center in the Southwest of United States of America, starting from day of transplantation ending at day 100 after transplantation.
2. Transplantation-related infection is operationally defined as an infection confirmed by: (a) positive culture from skin, nasal wash, blood, urine, or feces; (b) chest x-rays; (c) computed tomography (CT) scans; or (d) diagnosis by primary physician during the first 100 days post transplantation period.

3. Serum albumin is operationally defined as a measure of serum protein electrophoresis in one milliliter of whole blood with reference values ranging from 3.5-4.5 g/dL.
4. Body mass index (BMI) is operationally defined as a measure of weight in kilograms divided by squared of height in meter. As a continuous variable, BMI below 18.5 kg/m^2 is considered underweight, 18.5 to 24.9 kg/m^2 is normal weight, 25.0-29.9 kg/m^2 is overweight, and over 30 kg/m^2 is considered obese (Centers for Disease Control and Prevention, 2008).
5. Mucositis is operationally defined erythema, swelling, and ulceration of the oral mucous membranes. According to the World Health Organization (WHO) mucositis scoring system: (a) grade I, erythema; (b) grade II, painful ulceration, can eat; (c) grade III, painful ulceration, cannot eat; and (d) grade IV, painful ulceration, requiring parenteral support or opiate analgesics .
6. Pattern of weight recovery is operationally defined as a daily measurement of body weight in kilogram each clinical visit starting from admission to in-patient setting before transplantation and end at the last clinical visit before or on day 100.
7. Time of transplant is operationally defined as the day patient receives donor's stem cell infusion.
8. Graft-versus-host disease (GVHD) is operationally defined as stage one of signs and symptoms involving skin, liver, or gastrointestinal (GI) tract developing after BMT according to system for staging of GVHD proposed by Glucksberg et al. (1974) and revised by Thomas et al. (1975). Clinical sign of stage one skin involvement is defined as skin biopsy confirmation of a maculopapular eruption involving less than

25% of the body surface. An increased of 25% from normal bilirubin level is indicated as stage one of GVHD involvement in the liver. A loss of volume more than 500 ml per day of diarrhea is indicated as stage one of GVHD involvement in GI tract.

9. Relapse is operationally defined as more than 5% of blast cells count from bone marrow aspiration.

Limitations

Several limitations may affect the conclusions of this retrospective chart review study. The following limitations were identified as follows:

1. A nonprobability, convenience sample selected from a specific geographic location was utilized which limits the generalizability of this study to the sample drawn.
2. External events such as missing data, errors in data entry, season's clothing related to weather, or dehydration may influence the recording process and laboratory results.
3. The choice of selecting a homogenous sample of patients diagnosed with AML who received allogeneic BMT limits the generalizability of the finding.

Summary

Nutritional deficiency is a common problem among BMT recipients. Successful recovery from this complex and aggressive procedure depend on clinicians and nurses in recognizing individuals who have risk factors and existence of malnutrition. This study examined nutritional indicators that provide valuable information to help nurses identify patients who are at risk for nutritional deficiency so that intervention and referral can be initiated at the early stage of co-morbid cachexia.

CHAPTER II

REVIEW OF LITERATURE

Malnutrition is a frequent problem following blood and marrow transplantation (BMT). Early recognition of indicators of malnutrition offers the potential for interventions in order to improve the success of outcomes. The literature was searched for information related to malnutrition indicators related to morbidity and mortality among allogeneic bone marrow transplant recipients diagnosed with acute myeloid leukemia (AML). These patients are in the highest-risk group among all types of BMT because they received the maximum dosage from pre-conditioning regimens. It is anticipated that patients experience maximum toxicities from combination of cancer treatments.

A specialized database of MEDLINE citations provided by the National Library of Medicine, PubMed was selected as the primary source for this literature review. Other online database, such as CINAHL and ERIC were also reviewed. Extant knowledge from the reference lists of selected article were done by hand searched in the library. Abstracts from national conferences or seminars provided recent publications. Keywords or search terminology used are: cancer, allogeneic stem cell transplantation, myeloablative, acute myeloid leukemia, treatment, epidemiology, infectious complications, bacteria, virus, fungal, infections, mucositis, GVHD, relapse, survival, albumin, nutrition, body weight, weight changes, malnutrition, body mass index, mortality, morbidity, and cachexia.

Relevant information included in this review are categorized as follows: (a) acute myeloid leukemia; (b) myelodysplastic syndromes; (c) complications of allogeneic BMT; and (d) malnutrition indicators.

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults. The median age at diagnosis is 67 years, a disease associated with aging (SEER Cancer Statistics Review, 2007a). It is characterized by the proliferation of malignantly transformed hematopoietic stem cells of myeloid lineage (erythrocyte, megakaryocyte, monocyte, and granulocyte). These malignant cells accumulate in the bone marrow and lead to suppression of the growth and differentiation of normal blood cells. Symptoms are related to low production of mature red blood cells, platelets, and non-lymphocytic white blood cells (Devine & Larson, 1994).

Clonal chromosomal abnormalities can be detected in most cases of AML. Cytogenetic analysis is commonly used during diagnosis of AML in order to determine treatment strategies and prognosis. According to the French-American-British (FAB) classification, there are eight variants of AML (Bennett et al., 1985). More unfavorable chromosome abnormalities occur among elderly patients with AML than younger patients (Appelbaum et al., 2006).

When leukemia cells enter the peripheral blood, any organ system may become involved from leukemia-cell infiltration or metabolic complications related to leukemia such as pain or swelling in bones and joints, hepatomegaly, or splenomegaly (Wujcik,

2000). If acute leukemia is left untreated, patients suffer from anemia, uncontrolled bleeding, infection, and die within a few months.

Development of new chemotherapeutic and biologic agents in the past four decades has successfully generated appropriate therapeutic regimens. Currently, the overall 5-year relative survival rate for leukemia is 51.2% (SEER Cancer Statistics Review, 2007b). The goal of antileukemia therapy is to eradicate the neoplastic cells and restore normal hematopoiesis. Therapy is divided into remission induction and postremission therapy. Remission induction chemotherapy is designed to reduce the leukemia cell burden below the level of detection. A complete remission (CR) refers to a state where no leukemia cells are detected in the bone marrow and the peripheral blood counts have returned to normal. It is generally assumed that a substantial burden of leukemia cells persists, being undetected, leading to relapse within weeks or months if no further therapy were administered. Thus, postremission therapy is required in order to prevent relapse (recurrence) of AML (Devine & Larson, 1994).

A majority of elderly patients with AML are unable to receive further postremission therapy due to persistent treatment-related toxicities from induction therapy. A retrospective study done by Kantajian et al. (2005) found that only 454 of 998 (45%) elderly patients (over 65 years of age) achieved complete response and 285 patients (29%) died during remission induction period. The median survival time was 5.4 months (95% confidential interval: 4.4-6.3). The one- and two-year survival rates were 30% and 16%, respectively.

Only selected AML patients who achieved complete remission after induction therapy can proceed to postremission therapy. There are three treatment strategies for postremission therapy. First, consolidation therapy or early intensification refers to the administration of the same, more intense, or non-cross resistant chemotherapy used during induction. Second, maintenance chemotherapy, treatment that is generally less myelosuppressive and administered frequently over several months or years. Third, intensive myeloablative chemotherapy or chemoradiotherapy followed by marrow transplantation from an appropriate donor. Allogeneic BMT is preferred over autologous BMT due to the benefit of graft-versus-leukemia effect, an immune phenomenon in which donor lymphocytes recognize and eradicate residual host leukemia cells in order to prevent relapse (Devine & Larson, 1994).

Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) were formerly described as preleukemia diseases. Its incidence was first reported to Surveillance, Epidemiology, and End Results (SEER) Program in 2001. According to SEER data from 2001 to 2003, the risk of being diagnosed of MDS increased with age. The median age at diagnosed was 76 years. Men had a higher incidence than women. In 2003, approximately 10,300 incident cases were diagnosed in the United States. The prognosis of MDS patients was poor, with an observed 3-year survival rate of only 35% (Ma, Does, Raza, & Mayne, 2007).

MDS are a set of clonal stem-cell disorders characterized by ineffective hematopoiesis in one or more of the lineages of the bone marrow that arise from a generally unknown etiology. The diseases lead to varying degrees and combinations of

anemia, neutropenia, and thrombocytopenia, resulting in a dependence on transfusion, an increased risk for infection or hemorrhage, and a progression to AML (Fenaux, 2004).

The association of MDS with increasing age suggests genetic damage caused by hazardous exposure or inherited susceptibility. There are five subgroups of MDS proposed in the FAB system based on the number of ringed sideroblasts, degree of monocytosis, and percentage of myeloblasts. According to FAB classification, patient with less than 30% blast cells in bone marrow and peripheral blood with evidence of ineffective hematopoiesis were considered to have MDS, whereas AML was diagnosed when blast percentage exceed 30% (Corey et al., 2007).

Treatment for patients with MDS must be individualized because the disease and outcome of treatments are influenced by age and individual clinical factors. Standard treatment consists of supportive care such as transfusions to correct anemia, administration of hematopoietic growth factors, chemotherapy, and allogeneic BMT. Chemotherapy, same as used in AML, is limited to younger patients with more advanced disease. To date, allogeneic BMT is generally the only procedure with curative potential for patients with MDS (Fenaux, 2004).

Complications of Allogeneic BMT

The most common type of BMT is an allogeneic BMT, a transplant from someone other than an identical twin who has a human leukocyte antigen (HLA) identically or closely matched, commonly from sibling or an unrelated donor. The process includes a conditioning regimen of high-dose radiation and/or chemotherapy administration, stem cell harvest from a donor, stem cell infusion, and recovery. The post-transplant recovery

period is the most critical time in the BMT process (Saria & Gosselin-Acomb, 2007). A complete immune recovery may take up to 2 years after BMT (Hurley, 1997). Complications among post allogeneic-BMT recipients are related to: (1) pre-condition regimen toxicities; and (2) graft-versus-host disease (GVHD).

Pre-condition Regimen Toxicities

The myeloablative conditioning regimen during pre-transplant period depends on the host underlying disease. Common protocols for allogeneic BMT consist of high dose chemotherapy and total body irradiation (TBI) for 6 days before stem cell infusion (Poliquin, 1997). The goal of this "conditioning regimen" are : (a) to eradicate existing disease or malignant cells; (b) to suppress the recipients' immune system to prevent graft rejection; and (c) to create space within the host to allow transplanted cell engraft (Kamani & August, 1984). Patients begin to experience symptoms related to chemotherapy and radiation. Two complications related to pre-condition regimen will be focused on: (1) mucositis; and (2) infection.

Mucositis

Mucositis is a major debilitating side effect of high dose chemotherapy and/or radiation therapy during induction therapy and myeloablative therapy. The incidence of oral mucositis can be close to 100% among stem-cell transplant recipients. Adverse mucosal changes typically begin 4-5 days following chemotherapy infusion or a radiation dose of 10 Gy. The ulcers of mucositis resolve spontaneously within 2-3 weeks following the completion of treatment (Sonis, 2007).

The severity of oral mucositis varies from mild erythema to burning mucosal discomfort which interferes with eating, swallowing and speaking. This problem is often associated with xerostomia (dryness of the mouth) and taste alterations that lead to anorexia, weight loss, and weakness. A large area of deep ulcers may require a high dose of opioids for pain intervention. Severe inflammation and injury to the oral mucosa provides an entry for oral bacteria and increases the risk of systemic infection, especially among immunocompromised hosts like BMT recipients. These complications can complicate the treatment plan, extend hospital stay, increase costs related to antibiotics, and decrease the patient's quality of life (Silverman, 2007).

Bellm, Epstein, Rose-Ped, Martin, and Fuchs (2000) conducted a qualitative study using one-to-one in-depth interviews with one professional medical interviewer, to explore patients' experiences while undergoing the myeloablative conditioning regimen for BMT within 18 months of the scheduled interview. Thirty-eight participants (10 men, 28 women), age ranged from 20 to 64 years, were interviewed from five major metropolitan areas in the United States. Twenty-eight patients (74%) received autologous stem cell transplantation and 10 patients (26%) received allogeneic transplantation. An interview guide with a series of open- and closed-ended questions was used to have patients describe the side effects from his/her transplant experiences. Each patient was asked to select the most debilitating side effect.

Participants reported mouth sores as the single most debilitating side effect of BMT. Oral mucositis was selected by 16 patients (42%). Five patients (13%) reported nausea and vomiting. Fatigue and diarrhea were the least reported among three patients

(8%). All ten allogeneic transplant recipients (26%) reported a change in sense of taste during their transplants (Bellm et al., 2000).

Wardley et al. (2000) conducted a prospective study evaluating the clinical progress of oral mucositis among 365 patients undergoing myeloablative therapy BMT during 1985-1997. The majority of the patients (n = 236, 65%) received peripheral BMT. Sixty-seven patients (18%) received allogeneic-BMT. The World Health Organization (WHO) oral mucositis assessment was used to evaluate patients from day 1 (start of chemotherapy) to day 28, or day of discharge. Oral mucositis was experienced by 362 patients (99%) and 246 patients (67.4%) had grade III or IV toxicity. Strong opiate analgesia was prescribed for 173 patients (47%) for a median of 6 days.

Sonis et al. (2001) conducted a prospective, multinational study to explore the relationship between oral mucositis and selected clinical and economic outcomes among 92 hematopoietic stem-cell transplant patients from 8 cancer centers using a new Oral Mucositis Assessment Scale (OMAS). Eight regions of the oral cavity were evaluated for erythema and ulceration/pseudomembrane formation (using same rater for any given patient) beginning on the first day of condition regimen for 28 days or day of follow-up, whichever came first.

In general, allogeneic-BMT patients experienced worse clinical and economic outcomes when compared to the autologous-BMT patients. The incidence of oral ulceration was 88% (44 of 50) among allogeneic-BMT patients and 83% (35 of 42) among autologous-BMT patients. The mean hospital charges for the index admission were approximately $70,000 higher among allogeneic-BMT patients. The allogeneic-

BMT patient's peak OMAS scores indicating severity of mucositis were significantly correlated with hospital charges ($r = .57, p < .05$), TPN days ($r = .46, p < .05$), injectable narcotic days ($r = .44, p < .05$), and 100-day mortality ($r = .35, p < .05$) (Sonis et al., 2001).

Mucositis is a major complication to patient health and economic costs. Several attempts to prevent this condition had been reported. Methotrexate has been used as an antiproliferative GVHD prophylaxis agent. Its side effects included impaired mucosal regeneration, and worsened and prolonged mucositis. Cutler et al. (2005) reported a retrospective cohort analysis comparing outcomes related to mucositis among patients who received a sirolimus-based, methotrexate-free regimen (study group, ST group, $n = 30$) and a methotrexate-containing regimen (control group, TM group, $n = 24$) among allogeneic BMT. Data were collected from October 2000 to May 2003. Oral assessments were done three times weekly.

The incidence of severe (grade 4/5) mucositis was 50% in the TM group (12 of 24 patients) and 7% in ST group (2 of 30 patients). The median numbers of days with mucositis (more than grade 2 severity) among TM group were 9.5 days and 4.5 days among ST group, ($p = .008$.) The median numbers of days in using TPN among TM groups were14 days and 2 days among ST group, ($p = .005$.) The researchers concluded that the use of a sirolimus-based regimen improved mucositis and its adverse outcomes (Cutler et al., 2005).

In 2004, palifermin (KGF-1; Kepivance) was the first agent approved by the US Food and Drug Administration for prevention and treatment of mucositis induced by

conditioning regimens for hematopoietic stem-cell transplantation. Spielberger et al. (2005) conducted a multicenter (13 hospitals in USA), double-blind study to compare the effectiveness of palifermin to placebo in preventing oral mucositis among patients (N = 212) who received high dose chemotherapy and radiotherapy plus stem-cell transplantation. Subject enrollment was done during March 2001 to October 2007, with various hematological malignancies. All subjects received autologous stem cell transplantation following TBI and chemotherapy. The study group (n = 106) received palifermin intravenously for three consecutive days immediately before the initiation of conditioning regimen. Oral mucositis was evaluated daily for 28 days after transplant.

The incidence of oral mucositis (WHO grade 3 or 4) was 63% (67 of 106 patients) among the palifermin group and 98% (104 of 106 patients) among the placebo group, $p <$ .001. The median duration of mucositis (WHO grade 3 or 4) was six days and 9 days among palifermin and placebo group, respectively, ($p <$ .001) (Spielberger et al., 2005).

Mucositis is considered a major complication that affects the oral intake and nutrition status among allogeneic BMT recipients. According to above findings, allogeneic BMT recipients are at high-risk for mucositis. Oral ulceration can be a contributing factor for bacterial colonization and other secondary infections. Information related to the use of palifermin, after approval by FDA in 2004 will be considered during this chart review so that uniform treatments among BMT recipients are compared. The early sign and symptoms related to mucositis can be missed or diagnosed as acute GVHD.

Infection

Post BMT recipients are at risk of all types of infection due to the delayed recovery of both cellular and humoral immunity. Bacterial and fungal infections are the predominant cause of infections during the first 30 days after transplantation. The incidences of viral and fungal infection increase during 30-100 days, the period of neutrophils recovery and the use of high-dose corticosteroids for acute GVHD. Opportunistic infections from bacteria, fungi, protozoa, and viruses continue after 100 days when patients discontinue immunosuppressive therapy and suffer from chronic GVHD (Pallera & Schwartzbert, 2004). The literature review in this study will focus on complications of infection during the first 100-day post BMT.

Prophylaxis with a broad spectrum of antibacterial, antiviral, and/or antifungal agents are routinely prescribed during post-BMT recovery period (100 days) (Hurley, 1997). The risk of infection is determined by the selected transplantation modality. Patients who received allogeneic BMT are at a much higher risk of infection due to the myeloablative conditioning regimen and have a longer recovery of immune function when compared to those with non-myeloablative regimen (Junghanss et al., 2002).

An infection in the pre-engraftment period (the first 30 days) is mainly determined by the duration and severity of neutropenia. Other risk factors for infectious complications are: (a) extensive mucosal damage as a result of the conditioning treatment; (b) bacterial colonization; (c) local fungal and viral infections; (d) reactivation of infections that have been acquired during previous neutropenic periods while receiving induction therapy; and (e) the use of central venous catheters (CVC). *Gram-positive*

infections are mainly associated with CVC and most frequent in patients with severe mucositis. *Gram-negative* pathogens enter the bloodstream through damaged mucosa of the gastrointestinal tract in patients with severe gastrointestinal mucosal damage (Einsele et al., 2003).

Viral infection in the early period is rare due to prophylaxis antiviral therapy. However, in seropositive patients with inadequate antiviral prophylaxis, Herpes Simplex Virus (HSV) is the most common early infection following BMT (Einsele et al., 2003) usually in the form of gingivostomatitis. HSV pneumonia can be developed by contiguous spread from oropharynx to the trachea, resulting in viremia and pneumonia (Soubani, Miller, & Hassoun, 1996). Community respiratory viral infection such as an influenza virus can subsequently lead to interstitial pneumonia (Whimbey et al., 1996).

Candida (non-mould) and *Aspergillus* (mould) species are the most frequent pathogen caused systemic fungal infections among post BMT recipients. *Candidal* infection often occurs in the earlier recovery period of post BMT, but is rarely the sole cause of pneumonia. The portal of entry of this pathogen is the gastrointestinal tract or indwelling venous catheters (Soubani et al., 1996). *Aspergillosis* frequently occurs after day 100. However, clinical risk factors associated with Aspergillosis before day 40 post BMT are: (a) old age; (b) advanced hematological malignancy; and (c) the use of bone marrow or cord blood instead of peripheral blood stem cell (Marr, Carter, Boeckh, Martin, & Corey, 2002).

Oral infection. The conditioning regimen induced neutropenia and defects in mucosal and cutaneous barriers generate favorable conditions for existing organisms in

the oral cavity to enter the bloodstream, causing systemic infection. Epstein, Hancock, and Nantel (2003) conducted a prospective study to examine the relationship between oral colonization by the *Candida* species and systemic infection, mortality, and the impact of antifungal treatment on BMT recipients in Canada. One hundred and fifteen consecutive BMT patients, admitted during January, 1995 to December, 1996, were evaluated. Patients were conditioned by using various protocols depending on the disease and transplant types. Oral examinations and cultures for *Candida* were done before transplantation and weekly during hospitalization until 4 weeks after transplantation or discharge. Oral mucositis was assessed by using National Cancer Institute (NCI) Common Toxicity Criteria, version 2.0.

Seventy-four percent of patients (86 of 115) developed ulcerative mucositis (NCI grade 2 or higher). Colonization of *Candida* species was identified in 31% patients (36 of 115) with 34 allogeneic and 2 autologous BMT. Fifty-six percent of patients (20 of 36) had clinical evidence of oral *candidiasis*. Twenty-five patients died in the immediate post-transplant period; 68% of patients (17 of 25) were *Candida*-positive of the nine autopsies performed, 8 patients had documented systemic *Candida* infection. Patients who had evidence of *Candida*-positive colonization before transplantation and underwent TBI were more likely not to survive the transplantation when compared to those who were *Candida*-negative ($p < 0.001$). In patients undergoing systemic antifungal prophylaxis, a combination of using chlorhexidine rinse and nystatin was statistically more effective in reducing *Candida* colonization than using chlorhexidine alone ($p <$ .046) (Epstein et al., 2003). Oropharyngeal *candidiasis* was common among allogeneic-

BMT recipients who received myeloablative treatment (both chemotherapy and radiation). Oral mucositis continued despite systemic and topical antifungal prophylaxis. Therefore, the risk of systemic *candidal* infection remains high.

Central venous catheter infection. Another important port of entry for bacterial and fungal infection for the BMT recipient is the central venous catheter (CVC). Central venous catheters are routinely inserted and remained in every BMT recipient throughout the first 100 days post transplantation. CVCs are used to administer fluids, antibiotics, blood products, and alimentation, and for obtaining blood samples. Elishoov, Or, Strauss, and Engelhard (1998) conducted a 5-year prospective study of 242 BMT recipients to determine the incidence of bacteremia, fungemia, and other catheter-related infections, the causal pathogens, clinical course, and outcomes. Daily blood cultures were obtained from indwelling two-way CVCs, Hickman or Broviac catheter, from day -7 (pre-transplant) until discharge. The primary diseases among all subjects are malignant disease (209 patients), aplastic anemia (20 patients) and non-malignant diseases (13 patients). Subjects' age ranged from 1 month to 53 years. One hundred seventy-three patients received an allogeneic BMT and 69 patients received an autologous BMT.

Half of the patients (120 of 242) had 161 episodes of infection during the hospitalization period following BMT. Thirty-seven percent of patients (90 of 242) experienced 112 episodes of septicemia. Forty-five percent of septicemia episodes (51 of 112) were catheter-related septicemia. Neutropenia was found to be a risk factor. Seventy-five percent of septicemia (85 of 112), 65% of the catheter-related infections (65 of 100), and 90% of deaths (9 of 10) occurred during neutropenic periods (day -3 pre-

transplant and day +63 post-transplantation). There was a higher incidence of septicemia episodes during neutropenic period than during non-neutropenic periods. There were 17.82 septicemia episodes per 1,000 neutropenic days (85 episodes during 4,771 neutropenic days) versus 5.51 during the non-neutropenic days (27 episodes per 4,896 non-neutropenic days) ($p < .0001$) (Elishoov et al., 1998).

Of the 124 pathogens isolated from septicemia episodes, 52% (64 of 124) were *Gram-negative* bacteria; 42% (52 of 124) were *Gram-positive* bacteria; and 5% were *Candida* species. There were 10 (4%) septicemia-related death in this study. Forty percent of the deaths (4 of 10) had catheter-related septicemia. *Pseudomonas aeruginosa* septicemia was involved in half of the deaths (5 of 10) (Elishoov et al., 1998). Post-BMT recipients who have venous catheters are at greater risk in developing catheter-related infection and systemic septicemia during their netropenic periods.

Respiratory tract infection. Respiratory tract infections among BMT recipients result from direct contact with infected family members, or healthcare providers. The mortality rate of respiratory viral infection is about 60% (Hebart & Einsele, 2004). Community respiratory viruses (CRVs) have been recognized as a potential cause of pneumonia and death among BMT recipients. Influenza, parainfluenza, respiratory syncytial virus (RSV), and picornavirus infection are common causes of upper respiratory infection (URI) (Whimbey et al., 1996). It is important to note the seasonal pattern of community outbreaks associated with these viruses so that preventing transmission from person to person in outpatient setting can be initiated.

Chemaly et al. (2006) conducted a retrospective study to review the microbiology laboratory records dated from July1, 2000, to June 30, 2002, to identify patients who had respiratory specimens positive for influenza, parainfluenza, RSV, or picornavirus. There were 343 infections among 306 adults (older than 17 years) diagnosed with hematologic malignancies and BMT recipients. Specimens were routinely collected from patients presenting with symptoms of a URI. Respiratory culture samples were collected from throat swabs, nasopharyngeal wash specimens, and, in some patients, tracheal aspirates or bronchoalveolar lavage specimens. The cultures sites were chosen by the attending physician. Patients were followed until resolution of all signs and symptoms of infection or death. Two primary endpoints were: (1) progression to pneumonia, and (2) death associated with infection due to RSV, influenza, or parainfluenza.

Influenza was isolated most frequently (33%, n = 112), with type A accounting for 21% (n = 72) and type B 12% (n = 40). RSV infection accounted for 31% (n = 107) of infections. Parainfluenza was isolated for 27% (n = 92) with type 3 accounting for 23% (n = 80). Infections caused by influenza, RSV, and picornaviruses were seasonal, occurring between November and April. Parainfluenza infections occurred throughout the year but often during April to June. Infection progressed to pneumonia in 35% of patient (n =119). The overall mortality rate for CRV pneumonia was 15% (n = 16) (Chemaly et al., 2006).

Most infections occurred in patients BMT recipients (67%, n = 230), and majority of those (73%, n = 168) were allogeneic BMT recipients. Patients with URI progressing to RSV pneumonia were older than 65 years (OR, 1.037; 95% CI, 1.001-1.074; p = .042).

The only independent predictor of fatal outcome was an absolute lymphocyte count less than or equal to 200 cells/ml (OR, 30.46; 95% CI, 1.39-666.29; $p = .03$) in patients with influenza pneumonia (Chemaly et al., 2006). The researchers concluded that BMT recipients who have known predisposing factors (age more than 65 years with absolute lymphocyte count less than 200 cells/ml) with URI related to influenza or RSV should receive antiviral therapy in order to prevent progression to pneumonia or death.

Graft-versus-Host Disease

Graft-versus-host disease (GVHD) is a major complication of allogeneic bone marrow transplantation with donor-recipient histocompatibility (Wujcik, Ballard, & Camp-Sorrell, 1994). It is a consequence of donor T-cells recognizing host-recipient antigens as foreign tissue. The primary targets for acute GVHD are: (a) skin; (b) gastro-intestinal tract; and (c) liver (Gale, 1985). Severity of GVHD depends on the degree of Human Leukocyte Antigen (HLA) incompatibility. The greater the disparity the HLAs, the greater the chance of rejection (GVHD) (Parr, Messino, & McIntyre, 1991).

Graft-versus-host disease is divided into an acute and chronic phases. Acute GVHD generally occurs between days 7-50 after transplantation (Vogelsang, Hess, & Santos, 1988). Chronic GVHD appears after transplantation day 100. The disease resembles autoimmune disorders. It is triggered primarily by loss of autologous regulation of immunity (Gale, 1985).

Weisdorf et al. (1990) conducted a retrospective analysis of the long term clinical outcomes and complications of 469 recipients of sibling donor, allogeneic-BMT between January, 1979 and October, 1987. One hundred ninety-seven patients (42%) developed

greater than or equal to grade II acute GVHD between days 9 to 98, with a median of 38 days post BMT. After treatment with corticosteroids or other immunosuppressive therapies, 138 patients (70%) developed chronic GVHD. Graft-versus-host disease was a major contributing cause of death in 49 of the 90 patients (54%) who died from secondary complications of infection or interstitial pneumonitis.

Sullivan et al. (1991) reported the incidence of chronic GVHD among 1,431 patients with hematologic malignancies who received allogeneic-BMT who survived at least 150 days after transplantation. Chronic GVHD occurred in 377 of 1143 patients (33%) who received a BMT from HLA-identical siblings; 107 of 219 patients (49%) who received aBMT from HLA-nonidentical family members; and 44 of 69 patients (64%) who received a BMT from unrelated donors, respectively.

Kernan et al. (1993) conducted an analysis to evaluate the engraftment, acute GVHD, and chronic GVHD among 462 patients who received transplantation from unrelated donors facilitated by the National Marrow Donor Program. The transplantations were performed at 28 transplantation centers in the United States. The engraftment occurred at a median of day 22 after transplantation. The incidence of grade II, III, or IV acute GVHD was 64%, and chronic GVHD at one year was 55%. Patients with leukemia were followed for a median length of 1.5 years. The disease-free survival at two years among patients with leukemia was 40% with good prognostic factors, and 19% among high risk patients.

Prevention of acute GVHD has customarily involved post-grafting immunosuppressive therapy. A combination of methotrexate and cyclosporine is also

used to prevent GVHD (Storb, 1989). Prednisolone is used at the first sign of acute GVHD in order to reduce the severity of the disease (Ringden et al., 1983). The most effective drug to treat chronic GVHD is prednisolone, given either single agent or in combination with cyclosporine (Storb, 1989). The treatment of GVHD enhances the vicious cycle of GVHD, immuno-suppression, and increased susceptibility of infection (Lum, 1990).

Prolonged usage of immuno-suppressive medications are associated with many metabolic/nutritional side effects (Perez, 1993). Corticosteroids are involved in metabolic alterations which include significant protein catabolism (with high dosage), hyperphagia, insulin resistance with hyperglycemia, hyperlipidemia, calciuria (Perez, 1993), fluid and sodium retention, and gastrointestinal ulceration (Hasse, 1993). Methotrexate therapy is associated with alterations in taste, irritability, tiredness, light-headedness, and headache due to folic acid deficiency (Duhra & Foulds, 1988). Fever, nausea, vomiting, and mucositis are also reported (Dreizen, Bodey, & Rodriquez, 1975). Cyclosporine side effects are related to hepatotoxicity, nephrotoxicity, elevated serum creatinine level, hyperuricemia, mild anemia, infection, ocular inflammation, and central nervous system toxicity (Palestine, Nussenblatt, & Chan, 1984). Cyclosporine is known to cause hypertension, hypomagnesemia, and real magnesium wasting in BMT recipients. Magnesium replacement has been recommend in the treatment and/or prevention of cyclosporine-associated hypertension (June, Thompson, Kennedy, Loughran, & Deeg, 1986).

The incidence of gastrointestinal GVHD involvement is very important because it directly relates to nutritional intake and infection among BMT recipients. Toxicities related to medication side effects used for GVHD prophylaxis and its treatment can contribute to decreased albumin levels, an indicator for malnutrition assessment.

Malnutrition Indicators

Nutritional Problems among BMT Patients

Nutritional status throughout the course of BMT is often compromised due to the cytotoxicity of conditioning regimens and the side effects of multiple prophylaxis medications. As mentioned previously, many of these medications cause gastrointestinal discomfort, electrolyte imbalance, and organ dysfunctions. Therefore, BMT recipients often have decreased oral intake, increased nutritional requirements, and impaired nutrient utilization (Kilmartin, Rappeport, & Holmes, 2001).

Lessen et al. (1990) conducted a retrospective chart review among 192 post-allogeneic BMT recipients who were alive, disease-free, and had returned for long-term follow-up 1 year after transplantation. Data were collected from medical records between January, 1982 and July, 1984. The purposes of this study were: (1) to identify the prevalence of nutrition-related problems; and (2) to provide descriptive data about the nutritional status of long-term survivors of allogeneic-BMT. Among these patients, 65 (34%) were children younger than 18 years old and 127 (66%) were adults, 18 years or older.

At the one-year follow-up, the dietitian interviewed patients regarding vitamin and mineral supplementation, appetite, weight changes, taste alterations, oral sensitivity

and dryness, nausea, vomiting, gastric reflux, dysphagia, abnormal stool output, and exercise tolerance. A diet history was obtained using food models and the food frequency method of diet recall for the previous month's intake. Protein and energy intakes were estimated by computer analysis. Nutritionally relevant laboratory data were collected, including potassium, magnesium, glucose, and renal and liver function tests (Lenssen et al., 1990).

Reported weight loss was the most commonly cited problem (28%, $n = 54$). However, the degree of patient-reported weight loss was not quantified in this study. Oral sensitivity was a complaint among 23% ($n = 45$) of all patients. The frequency of xerostomia was 18% ($n = 34$); anorexia 8% ($n = 15$); gastric reflux 7% ($n = 13$); diarrhea 7% ($n = 13$); steatorrhea 5% ($n = 9$); dysgeusia 3% ($n = 5$); and limited exercise tolerance because of dyspnea or joint contractures 4% ($n = 8$). At one year post transplant, 24% ($n = 20$) of patients who weighed less than 90% of their ideal body weight displayed extensive chronic GVHD. There was a greater prevalence of elevated serum liver function tests (more than twice normal value) and depressed serum albumin among patients with extensive chronic GVHD. Patients with extensive GVHD ($N = 85$), 40% ($n = 34$) reported inadequate energy intake (less than 85% of estimated energy requirement) (Lenssen et al., 1990). The researchers concluded that a high prevalence of nutritional problems among recipients of allogeneic BMT 1 year after transplantation and suggested the need for an ongoing, community-based nutrition monitoring after discharge from a transplant center (Lenssen et al., 1990).

Stern (2000) conducted a randomized, controlled trial to determine whether adult patients who received marrow transplants and were discharged earlier from hospital to an ambulatory setting with no or minimal oral energy and nutrient intake (ambulatory group) would resume oral intake faster and require shorter duration of intravenous (IV) fluid than patients remaining in the hospital (control group). Data were collected from July 1989 through August 1991. Patients who had oral energy intake less than 33% of the estimated energy requirement and requiring up to 3,000 ml of IV fluid per day were selected for this study. Subjects were assigned randomly to remain hospitalized as a control group ($n = 40$) or discharged to an ambulatory setting ($n = 38$).

Participants received nutrition counseling by a registered dietitian to promote resumption of oral intake. The two groups were evaluated to determine the number of days after study entry to: (a) consume 33% of the oral energy requirement for 3 consecutive days; (b) require no parenteral nutrition; and (c) require no IV hydration. The 3-day period was chosen to confirm the oral intake could be maintained by the patient. The 33% level was chosen as a level of intake that suggested GI tolerance of oral nutrients. Intakes were reported as the proportion of total estimated energy or protein requirement (Stern et al., 2000).

The hospital group took fewer days than the ambulatory group to resume 33% oral energy requirement for 3 consecutive days (4.5 vs 8.0, $p = .004$) and to discontinue all IV fluids (30.5 vs 48.5, $p = .019$). The researchers concluded that earlier hospital discharge could achieve cost saving but may delay resumption of oral energy intake. Nutrition assessment and counseling are necessary in both hospital and ambulatory

settings to promote resumption of oral intake and discontinuation of intravenous fluid because BMT patients are in a high risk for poor nutritional status and for potential rapid change in medical status (Stern et al., 2000).

In addition to the physical complications, there are financial and psychosocial problems associated with BMT. Transplant recipients often are treated at advanced medical facilities far from home. The cost of maintaining a second home near the treatment centers, loss of job and income, and non-covered cost of medical bills from health insurance carrier add to financial burdens that patients and families had to absorbed during outpatient visits. The stress of being treated for fatal illness, long-term isolation, side effects from treatments, and painful procedures, can cause patients to become dependent, angry, refusal to cooperate with healthcare staffs (Kamani & August, 1984), and loss hope for full recovery.

Body Weight, Weight Loss and Body Mass Index

Body weight and height are routinely the initial pieces of nutrition assessment data recorded on admission to the hospital or during an outpatient visit. These body measurements are taken into consideration for dose calculations for chemotherapy, total body irradiation, anti-viral, and anti-bacterial prophylaxis therapy. Changes in body weights can influence the treatment decision and outcomes among cancer patients.

Adjustments are made according to body-frame size for obese patients. Radiotherapy dosage and using tissue blockages for vital organ are considered during total body irradiation (TBI) in obese patient by accommodating the large body contour and adipose tissue in order to maximize effectiveness of radiotherapy. In obese patients,

chemotherapy dosage is determined by using ideal body weight rather than current weight in order to avoid excessive organ toxicity from overdosing (Ritchie, Wirth, & Grigg, 2001).

The formula for calculating ideal body weight (IBW) in adults is based on the individual's height. For men, IBW is equal to 106 pounds (lb) plus 6 lbs for each inch over 5 feet. For women, IBW is equal to 100 lb plus 5 lb for each inch over 5 feet. The current body weight of an individual is then divided by the IBW and multiplied by 100 to yield %IBW (Evans-Stoner, 1997).

Deeg, Seidel, Bruemmer, Pepe, and Appelbaum (1995) studied the impact of body weight on acute toxicity post-BMT through day 150. Data were collected from 2,238 patients (1,662 adults, 576 children) who received BMT from January 1985 to January 1992. Adults (older than 18 years) and children (younger than 18 years) were considered separately. According to the demographic information of both groups, subjects had various types of diseases (malignant and non-malignant) and received different types of transplantation. Patient weights were recorded at the time of initial evaluation before transplantation and before starting the conditioning regimen. Patients' weights were calculated as percentage of IBW and grouped into 4 weight categories: (a) < 85%; (b) 85-95%; (c) 95-145%, and (d) > 145%.

Survival by weight category was summarized by means of Kaplan-Meier curves. Log rank statistics were used to compare survival between the categories. Survival among adults when all groups compared to 95-145% IBW indicated that patients in the < 85% IBW category had the worse survival rate ($p = .0001$) followed by 85-95% IBW

category (p = .0004). Subjects in >145% IBW category were slightly but not significantly lower than 95-145% IBW category (p = .29). The survival among children was similar but did not reach statistical significance when all groups were compared to 95-145% IBW category (<85% IBW category, p = .22; 85-95% IBW category, p < .01; >145% IBW category, p = .66) (Deeg et al., 1995).

Researchers used Cox regression analysis to assess the significance of weight as a risk factor for overall and non-relapse mortality using nine covariates which were known or suspected as risk factors. These risk factors were: (a) patient sex, (b) race, (c) age, (d) diagnosis/disease status, (e) type of transplant, (f) year of transplant, (g) dose of TBI, (h) GVHD prophylaxis, and (i) acute GVHD. Adults patients with <85% IBW had significantly higher risk (RR = 2.11, p < .01). Patients with 85-95% IBW and >145% IBW showed elevated risk (but not significantly), (RR 1.26, p = .07, and RR = 1.33, p = .11, respectively). For children, only 85-95% IBW group yielded significant higher risks, (RR = 1.96, p < .01). The authors concluded that overweight patients did not have a significantly higher risk of death in non-relapse or overall mortality related to BMT. In contrast, severely underweight patients had a significantly worse prognosis than overweight patients. (Deeg et al., 1995).

Fleming, Rayens, and Garrison (1997) also used IBW to determine the impact of obesity on survival rate after high-dose therapy followed by allogeneic stem cell transplants. A retrospective, matched case-control, at a single institution was conducted to collect data from 322 patients who received a BMT from April 1983 to June 1995. Patients were categorized as either obese (>120% IBW) or non-obese (<80% IBW).

According to demographic information, all subjects had various types of disease (malignant and non-malignant). Kaplan-Meier curves were generated to display all survival distributions.

The overall survival among the obese ($n = 91$) and non-obese ($n = 231$) were 24% and 35% respectively ($p = .0045$). When subjects were separated by age, overall survival among 240 adults (16 years or older) were 16% and 30% for obese and non-obese, respectively ($p = .003$). The survival among 82 children (younger than 16 years) was not significantly different, 67% for obese and 46% for non-obese ($p = .24$) (Fleming et al., 1997).

When patients were stratified according to donor status, obese patients in both groups had inferior outcomes. Histocompatible transplant patients had an overall survival of 14% and 37% for obese and non-obese, respectively ($p = .0007$). Among non-histocompatible patients, the survival for obese and non-obese were 27% and 33% respectively ($p = .35$). Cause of death with relapse in both groups was not significantly different between obese and non-obese, 17% and 23%, respectively ($p = .461$). The researchers concluded that adult obese patients undergoing high-dose chemotherapy with allogeneic BMT had more adverse outcomes (Fleming et al., 1997).

The limitation of using IBW is that it does not reflect any changes in weight. Cumulative weight loss over time can lead to malnutrition. Calculating the percent of usual body weight (UBW), comparing the current weight with usual weight, reflects weight change and detects degree of malnutrition (Evans-Stoner, 1997). The intensity of condition regimen before BMT, as mentioned above, may reduce oral intake for a

prolonged period of time. Monitoring of nutritional status is an essential part of supportive care for patients who receive BMT.

Iestra, Febbe, Zwinderman, van Staveren, and Kromhout (2002) conducted a prospective study in the Netherlands to evaluate body weight recovery and compliance with dietary advice during the first year post-hospital phase after BMT. Only 69 adult patients (39 women and 30 men) completed all five time points questionnaire (day 50, 75, 125, 200, and 350) from May 1996 to November 1998. According to demographic information, subjects were heterogeneous, with various types of disease (malignant and non-malignant), and received either autologous or allogeneic BMT with or without TBI.

A logistic regression analysis was used to identify which baseline characteristics were prognostic factors for successful body weight recovery. After adjustment for pre-transplant weight (BMI > 25 kg/m^2), conditioning regimen (with or without TBI) was the only baseline characteristic that contributed significantly to predicting classification of body weight status at day 350 ($p < .05$; percent correct classification of the model 68%) (Iestra et al., 2002) .

Body weight recovery was analyzed for four subgroups characteristics by pre-transplant body weight status and conditioning regimen using a mixed-model analysis of variance ($N = 118$). There were lower percentages of patients who recovered at least 95% of their pre-BMT body weight among the group with TBI than the group without TBI at five time points (day 50, 75, 125, 200, 350). For normal weight patients with TBI (n =41), the percentages of patients with weight recovery at five time points were 36%, 20%, 28%, 41%, and 48% (respectively). Patients who had normal weight and did not

receive TBI (n =25), the percentages of weight recovery were 58%, 64%, 68%, 83%, and 88% (respectively). No p values were reported by authors in this section. The comparison information for the other two subgroups was not provided. Authors concluded that receiving TBI prior to BMT had negative effects to weight recovery among BMT patients (Iestra et al., 2002).

The human body restores the excess energy (calories from food) not used in daily physical activities as fat tissue. Body mass index (BMI) does not directly measure body fat but it correlates positively with the amount of body fat. It is defined as the weight in kilograms divided by the square of the individual's height in meters. This measure is then compared to the normal range among healthy people, indicating whether or not that person is over- or underweight. As BMI increases, the risk of disease and death related to overweight increases, such as cardiovascular disease, high blood pressure, osteoarthritis, cancer, and diabetes (Centers for Disease Control and Prevention, 2008).

Le Blanc, Ringden, and Remberger (2003) conducted a study to evaluate whether BMI was related to survival among allogeneic BMT recipients. Subjects were 544 adults, diagnosed with hematologic malignancies who received BMT from 1977 to August 2002. Patients were classified into three groups based on their BMI before transplantation: (a) underweight (BMI < 20); (b) normal weight (BMI 20-25); and (c) obese patients (BMI> 25). Weight categories were summarized by means of Kaplan-Meier curves. Log rank statistics were used to compare survival between the three categories. The Cox proportional hazard regression model for univariate and multivariate analysis was used to assess the significance for weight as a risk factor for transplant-related mortality (TRM),

relapse and chronic GVHD, while controlling for patient's age, donor, year of transplant, conditioning regimen, diagnosis, disease status, and stem cell sources.

The two most common causes of death were infection and relapse. The underweight group was found to have a statistically higher incidence of α-streptococcus septicemia ($p = .005$). The overall transplantation-related mortality (TRM) in the BMI <20 group was 47% which was significantly higher than TRM for patients of normal weight, 34%, ($p = .05$). The two most significant factors for TRM were BMT from an unrelated donor and a high-risk disease ($p < .01$). In multivariate analysis corrected for differences between the groups, the correlation between low BMI (<20) and high TRM was statistically significant (RH 1.46, CI 1.01-2.12, $p = .045$) (Le Blanc et al., 2003).

Body weight affected 5-year relapse-free survival, 34%, 41%, and 46% among three groups (BMI <20, 20-25, and >25), respectively (no p value reported). In corrected multivariate analysis, low BMI (<20) was correlated to a lower relapse-free survival (relative hazard [RH] 1.35; confidence interval [CI] 1.01-1.80; $p < .05$). Patients with a low BMI tended to have a lower 5-year survival, 36%, 47%, and 55%, respectively, ($p = .01$). In the corrected multivariate analysis, death was associated with low BMI (<20) (*RH* 1.42, *CI* 1.06-1.90, $p = .023$). Authors concluded that a low BMI (<20) was significantly correlated with an increased TRM, a decreased survival, and relapse-free survival after allogeneic BMT. The authors recommended considering BMI <20 as a risk factor when analyzing outcomes related to allogeneic BMT (Le Blanc et al., 2003).

Navarro et al. (2006) performed a retrospective cohort study of individuals undergoing autologous BMT for Hodgkin or non-Hodgkin lymphoma by using a database from the Center for International Blood and Marrow Transplant Research (CIBMTR) to evaluate the effect of BMI on survival, relapse, and toxicity. This study included 4,681 patients who underwent autologous BMT in 192 transplant centers from 1990 to 2000. Patients were divided into four groups by weight based on BMI as follow: (a) underweight (BMI < 18); (b) normal weight (BMI 18-25); (c) overweight (BMI > 25-30); and (d) obese (BMI > 30). Outcomes of this study were categorized as primary and secondary end points. Four primary end points were transplantation-related mortality (TRM), relapse, lymphoma-free survival (LFS), and overall survival. Four secondary end points were the incidence of infection, organ toxicity, secondary malignancies, and median days of hospitalization. Multivariate analyses used Cox proportional hazards regression models to compare the outcomes among the four weight groups to normal BMI (baseline group) while adjusting for all covariates (patient-, disease-, and transplant-related factors).

Transplantation-related mortality (TRM) was defined as death within the first 28 days of transplantation from any cause or death in continuous complete remission at any subsequent time point. In multivariate analysis of TRM using normal weight patients as the reference, the underweight group had a higher risk of TRM (relative risk [RR], 2.45; 95% confidence interval [CI], 1.58-3.81; $p < .0001$). Relapse was defined as the time to onset of clinical recurrence, disease progression, or persistent disease (at day 28). In

multivariate analysis, no differences of relapse risk were observed. Data were not available in the article (Navarro et al., 2006).

Lymphoma-free survivor (LFS) was defined as survival in continuous complete remission of primary disease, disease relapse, persistence, or death. In multivariate analysis, using normal weight patients as the reference, the underweight group had a higher risk of treatment failure (inverse of LFS; R*R*, 1.37; 95% CI, 1.11-1.71; $p = .004$). The overweight group had a lower risk of treatment failure (RR, 0.91; 95% CI, 0.83-0.98; $p = .02$) (Navarro et al., 2006).

Overall survival was defined as time to death from any cause. In multivariate analysis, using normal weight patients as the reference, the underweight group had a higher risk of mortality (RR, 1.49; 95% CI, 1.17-1.89; $p = .001$). The overweight and obese groups had lower risk for mortality (RR, 0.87; 95% CI, 0.79-0.96; $p = .004$; and RR, 0.76; 95% CI, 0.67-0.86; $p < .0001$, respectively) (Navarro et al., 2006).

The underweight group had higher incidence of pulmonary and liver toxicity, and longer hospital stays when compared to the other three groups. The incidence of pulmonary toxicity among underweight, normal weight, overweight, and obese were 33%, 22%, 19%, and 20%, respectively ($p = .002$). The incidence of liver toxicity, including veno-occlusive disease (VOD) were 18%, 13%, 12%, and 11%, respectively ($p = .03$). The median hospital stays were 23 days, 21 days, 21 days, and 21 days, respectively ($p = .034$). The researchers concluded that underweight group had higher TRM rate, poorer LFS, and overall survival rate when compared to normal weight,

overweight, and obese group. Obesity alone should not be considered as a contraindication to BMT (Navarro et al., 2006).

Serum Albumin Deficiencies among Patients with Cancer

Serum albumin is the major protein totally synthesized by the liver. Albumin serves in the plasma to maintain osmotic pressure and as a carrier of metals, ions, fatty acids, amino acids, metabolites, bilirubin, enzymes, drugs, and hormones. No pathologic conditions cause the liver to produce extra amount of albumin. Therefore, hyper-albuminemia is usually a result of acute dehydration. The most important factor regulating albumin synthesis is nutrition. Hypoalbuminemia is not seen in acute liver failure or starvation because its half-life is 20 days. It requires several days or weeks of lack of production before serum albumin drops (Rothschild, Oratz, & Schreiber, 1972a). An increased catabolism – such as that found in cancer, decreased liver function, surgery, infection, loss in body fluid from burns or wounds, hypothyroidism, or other hepatic toxins can contribute to a decrease in albumin production (Rothschild, Oratz, & Schreiber, 1972b). In this study, albumin can be useful for patients being followed over an extended time period.

Eriksson, Cederholm, and Palmblad (1998) evaluated the relationship between nutritional variables (body mass index, weight, and serum albumin) and susceptibility to infections (fever and neutropenia) among patients with acute leukemia during the induction therapy for the first remission. The full records of 52 patients with acute leukemia (29 males and 23 females) were part of a multicenter trial of various antileukemic and anti-infectious treatments in Sweden during 1980-1984. A serial

measurement of body weight; body mass index; serum concentrations of albumin; and days and weeks with fever, neutropenia and infection were obtained on a weekly basis from patient records.

During the induction period, patients lost a mean of 5.1 kg of body weight, corresponding to a reduction of body mass index. The changes in weight were significantly related to the number of days with fever (r = -.35, p = .026). Weight changes also correlated with the changes in serum albumin (r = .36, p = .03). Nearly half of the patients (47%, n = 24) developed severe hypoalbuminemia (< 25 g/L). The duration of hypoalbuminemia was significantly correlated with the duration of fever (r = .71, p = < .001) (Eriksson et al., 1998).

When days with fever was chosen as dependent variable in the multiple regression analysis, days with severe neutropenia and a drop in serum albumin were the most strongly associated predictors (r = .57, p = .0004 and r = .70, p = .003, respectively). Hypoalbuminemia turned out to be a prognostic factor for weight loss. When using change in weight as a dependent variable, change in serum albumin levels was the only independently related variable (r = .37, p = .03). Researchers concluded that adults patients with acute leukemia undergoing intensive cytotoxic treatment for induction of the first remission often have moderate weight loss and a high incidence of severe hypoalbuminemia, indicating a negative protein-energy balance (Eriksson et al., 1998).

Combinations of cytotoxic agents as part of cancer treatment are commonly used practices in order to improve survival among patients with cancer. Many of these agents are transported by binding with plasma proteins, such as albumin. Patients with

hypoalbuminemia are at a higher risk of developing complications from treatment related toxicities. Arrieta et al. (2010) conducted a prospective study from 100 consecutive subjects (53 males and 47 females) recently diagnosed with stage IV advanced non-small cell lung cancer (NSCLC) treated with first-line palliative chemotherapy, paclitaxel (TXN) and cisplatin (P) at Thorax Neoplasms Clinic in Mexico City from January 2007 to February 2009. The purpose of this study was to investigate the connection between malnutrition and serum albumin with the occurrence of chemotherapy-induced toxicity. Malnutrition was assessed using Subjective Global Assessment (SGA) prior to treatment. The Neutrophil Lymphocyte Ratio (NLR) and the Platelet Lymphocyte Ratio (PLR) were used to determine the presence of systemic inflammatory response (SIR) and were related to the development of toxicity. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria of Adverse Events (NCI CTCAE) version 3.0 after two chemotherapy cycles (Arrieta et al., 2010).

Subjects were placed into three categories according to SGA appraisal: (a) well-nourished (49%); (b) moderated malnourished (34%); and (c) severely malnourished (17%). Half of subjects (50%) had hypoalbuminemia (less or equal to 3.0 mg/ml). Subjects, who were moderately or severely malnourished and had hypoalbuminemia, developed more chemotherapy-induced toxicity overall when compared with patients without malnutrition (31 versus 22, $p = .02$) and normal albumin (mean rank, 62 versus 43, $p = .002$), respectively. NLR (above or equal to 5) was associated with basal hypoalbuminemia (mean ranks 55.7 versus 39 = $p = .006$). PLR (above or equal to 150) was significantly related to hypoalbuminemia (58.9 versus 41.3, $p = .02$). Researchers

concluded that chemotherapy-induced toxicity in NSCLC patients treated with TXN and P was associated with malnutrition and hypoalbuminemia (Arrieta et al., 2010).

Prolonged survival time with maximum patient quality of life and minimum treatment toxicities are common goals for cancer treatment. Prognostic factors become important issues in decision making of palliative chemotherapy when cancer is diagnosed at a late stage. Zacharakis et al (2010) conducted a retrospective chart review from 541 consecutive medical records from a single center in Greece. All subjects (298 males and 243 females) were diagnosed with stage IV metastatic colorectal cancer (CRC) from 1998 to 2008 and received non-surgical, palliative chemotherapy (single or combination agents). Thirty-seven variables were tested for their potential predictors of survival.

Mean survival time was recorded at 12.8 months [95% confidence interval 12.0-13.5]. Two hundred and seven subjects (38.3%) had weight loss of more than 10%. One hundred and one subjects (18.7%) had hypoalbuminemia. Eight factors independently associated with unfavorable to survival were: (a) decreased performance status; (b) C-reactive protein (CRP) > 5 mg/dl; (c) anemia; (d) anorexia; (e) weight loss more than or equal to 10%; (f) fatigue; (g) hypoalbuminemia; and (h) blood transfusions (Zacharakis et al., 2010).

According to the hazard ratio of risk factors, patients with weight loss more or equal to 10% had 3.3-fold higher probability of death than patients without weight loss (no *p* value provided). Patients with hypoalbuminemia had 1.27 times higher probability of death than those without this condition (no *p* value provided). The authors concluded that patients who are relatively fit, have low CRP levels, and tolerate a combination of

chemotherapy appear to have a more favorable survival outcome (Zacharakis et al., 2010).

Summary Review of Literature

Acute Myeloid Leukemia (AML) is a disease associated with aging. The treatment options are initially inducing the first remission by induction therapy and then followed by blood and marrow transplantation (BMT), preferably allogeneic-BMT. The main challenges associated with treating AML are: toxicity of the treatment or the treatment's lack of efficacy leading to relapse. Both induction therapy and BMT induce severe neutropenia that put patients at risk for infection, the leading cause of death besides relapse. Mucositis, the most common side effects from the conditioning regimen, leads to inadequate of oral intake and systemic infection from common pathogens in oral cavity. Graft-versus-host disease (GVHD), an expected complication from BMT, treated by initiating the use of steroids that lead to further metabolic problems and additional risk for infection. Older age and neutropenia are the major risk factors associated with infections. Malnutrition is also known to be associated with infectious complications and poor survival time among cancer patients. Many researchers identified malnutrition indicators among BMT recipients. These include body mass index (BMI), ideal body weight (IBW), weight loss, and serum albumin alterations.

CHAPTER III

PROCEDURE FOR COLLECTION AND TREATMENT OF DATA

A descriptive, retrospective design was used to guide a chart review examining factors associated with complications following bone marrow transplantation (BMT). Descriptive retrospective studies examine an existing phenomenon in present that was linked to phenomena that occurred in the past. The researcher begins with an outcome variable of interest (dependent variable) and then correlates it with one or more antecedent factors (independent variables). The process is used to identify risk factors that predicted outcomes (Polit & Beck, 2008b). In this study, the outcomes of allogeneic-BMT (transplantation-related infections and mortality) were linked to malnutritional indicators (BMI, body weight, and serum albumin) among post-allogeneic BMT recipients. This chapter presents information regarding the setting, population and sampling, protection of human subjects, data collection, and treatment of data.

Setting

This study was conducted in a cancer institution located in a large medical center in the Southwestern U.S. Approximately 150 of 680 patients receive myeloablative, allogeneic-BMT in this institution every year. Patients diagnosed with different types of cancers are treated at this institution with different protocols. Prior to BMT, patients are admitted to the hospital during the conditioning regimens and discharged to outpatient setting after engraftment and followed up to days 100 post transplantation.

Population and Sample

A convenience sample of information donors (charts) which met the following criteria were selected for this study: (a) 18 years of age or older; (b) diagnosed with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS); (c) completed information during myeloablative conditioning regimens and follow up for at least 80 days post transplantation at this institution; and (d) provided consent for the use of information in future research. The researcher reviewed information and lab results from 110 patients' electronic medical records starting from August 2005 to June 2008 using institutional computer. The sample of 110 was estimated using an alpha of .05, a power level of .80, and a medium effect size.

Protection of Human Subjects

Approval for this study was obtained from the Human Subject Review Committee of the participating cancer institution in this study and the Texas Woman's University. Approval letters are in appendices A and B. Only charts having consent from BMT patients to use their information for future research were reviewed for this study. Confidentiality of information was maintained by using code numbers on all study forms rather than patient's name. The demographic and data collection sheet (appendix C) used for this study will be saved for 5 years in a locked cabinet. Following the 5-year period or within 2 years post publication this information will be destroyed.

Data Collection

A list of medical record numbers of eligible information donors was obtained from the institution's BMT health care team. Demographic data and other information from individual records were hand-searched through the institution's electronic medical records. Data were recorded using a demographic and a data collection sheet created for each information donor. Data from 110 records were transferred for analysis.

Treatment of Data

The Statistical Package for the Social Sciences (SPSS) version 15.0 was used for data analysis. Nominal demographic data were analyzed using frequency and percentages. Interval data were analyzed using means and standard deviations.

To answer research question one regarding weight and albumin patterns, Microsoft Excel was used to display the graphic pattern of changes in body weight and serum albumin levels of each patient starting from the day of transplant (Day 0) and ending at approximately 100 days post transplantation (or the last follow up at institution ambulatory setting). A line chart was used to show changes of values (body weight and serum albumin) over time during this study. Both horizontal and vertical axes of all graphs were fixed in equal interval spaces. The horizontal axis on the graph represented the length of time from Day0 to Day100. The vertical axis of the weight graphs used fixed weight intervals of 40 kgs. The vertical axis of the albumin graphs was fixed with the range of zero to 5.0 gm/dL. To keep albumin and weight graphs separated, weight graphs were printed on blue paper and albumin graphs were printed on green. A Q-methodology or Q-sort procedure was used to classify the weight graphs and serum

albumin graphs into groups with similar patterns. Three raters independently sorted the graphs (Polit & Beck, 2008a).

The analyses for research question two were divided into four tests. Fisher's Exact Test for two independent samples (2x2) was used to determine the differences between (a) malnourished subjects indicated by weight loss (yes versus no) and transplant related mortality (survive versus not survive) and (b) malnourished subjects indicated by serum albumin level (high risk versus moderate/low risk) and transplant related mortality (survive versus not survive) (Siegel & Castellan, 1988b). A *t-test* for independent samples was used to compare the differences between malnourished subjects indicated by weight loss (yes versus no) and transplant related infections (Gravetter & Wallnau, 2000b). A Kruskal-Wallis one-way analysis of variance by ranks was used to determine the differences among three groups of malnutrition indicated by serum albumin levels (high risk, moderate risk, and low risk) and transplant related infections, followed by 3 pairwise comparisons as post-hoc test (Siegel & Castellan, 1988a).

To answer research question three, Fisher's Exact Test for two independent samples (2x2) was used to determine the differences between BMI (low and high) versus transplant related mortality (survive versus not survive). To answer research question four, a *t-test* for independent samples was used to test the cumulative incidence of transplant related infections differences between two groups of subjects with mucositis (grade I-II versus grade III-IV).

For question five, a multiple regression with controlled variables was used to determine the predictive effects of malnutrition indicators (BMI and serum albumin) to

transplant related infection during the 100 days post BMT. The controlled variables were age of transplant recipients, time of transplant, development of acute GVHD, and relapse (Huck, 2000). For question six, a logistic regression was used to determine the predictive effects of malnutrition indicators (BMI and serum albumin) to mortality during the one year post BMT. The controlled variables were age of transplant recipients, time of transplant, development of chronic GVHD, and relapse during one year post BMT (Garson, 2010).

There were total of eight analyses in this study. Therefore, the alpha was adjusted to .00625 for each analysis. Additionally, with three pairwise post hoc comparisons alpha was then set at .0021 for each comparison (in research question two).

CHAPTER IV

ANALYSIS OF DATA

One hundred and ten electronic medical records of consecutively enrolled subjects receiving treatments for allogeneic-bone marrow transplantation (BMT) under one protocol from a single cancer treatment center were reviewed to examine factors associated with complications following transplantation. Information was retrieved from the day each subject received their transplantation until 100 days post transplantation and at the time of one year follow up. This retrospective analysis focused on information related to malnutrition indicators (body weight and serum albumin level) and contributing factors (mucositis) related to malnutrition among post allogeneic BMT recipients. The relationships and predictive effects of malnutrition indicators to morbidity (infection incidences) and mortality outcomes were also examined. This chapter presents a description of the sample and findings for the six study research questions.

Description of the Sample

A total of 117 electronic medical records were reviewed and 110 of these records met the study inclusion criteria. Table 1 reflects demographic characteristics. The sample was roughly split between males and females with a slightly greater number of males. All patients received allogeneic transplants with approximately half of participants

receiving transplants from matched related donors and half from matched unrelated donors (MUD). Most subjects were diagnosed with acute myeloid leukemia (AML) while approximately one-fourth of subjects were diagnosed as having myelodysplastic syndrome (MDS). The means age of the sample was 46.6 (*SD* = 11.4). Most subjects were between the ages of 40 to 59 years of age with small representation from both younger and older age groups. Over 80% of subjects were Caucasian with a small amount of representation from Hispanics and African Americans.

Only nine subjects (8.2%) were not diagnosed with an infection during the first 100 days post BMT. The overwhelming majority of subjects (*n* = 101, 91.8%) in this study developed at least one episode of infection and the maximum number of infections was 14. The average number of infections diagnosed per patient was 4.35 *(SD*= 3.4). Over sixty-percent of patients experienced blood infections and more than half experienced urinary tract infections. In many incidences, the same site was infected with multiple organisms or reinfected with the same organism after cultures were cleared for some times. Table 2 displays sites of infection documented among this sample. The most common infections are specifically recorded with the 'other' category encompassing the following infection sites: appendix, gallbladder, testicles, duodenum, muscle, ear, bone, and teeth.

Table 1

Demographic Characteristics of BMT Sample

Characteristic	*f (%)*
Gender	
Male	58 (52.7)
Female	52 (47.3)
Total	110 (100.0)
Transplant Type	
Related	58 (52.7)
Unrelated (MUD)	52 (47.3)
Total	110 (100.0)
Diagnosis	
Acute Myeloid Leukemia	84 (74.4)
Myelodysplastic Syndrome	26 (23.6)
Total	110 (100.0)
Age	
20 to 29 years	15 (13.6)
30 to 39 years	16 (14.5)
40 to 49 years	21 (19.0)
50 to 59 years	51 (46.4)
60 to 69 years	7 (6.4)
Total	110 (100.0)
Ethnicity	
Caucasian	90 (81.8)
Hispanic	11 (10.0)
African American	5 (4.5)
Other	4 (3.6)
Total	110 (100.0)

Table 2

Sites of Infections During 100 Days Post BMT (n = 109)

Site	*f (%)*
Blood (Septicemia)	68 (61.8)
Urinary Tract Infection	57 (51.8)
Respiratory Tract Infection	51 (46.4)
Skin & Nails	40 (36.4)
Gastrointestinal Tract	36 (32.7)
Mouth	26 (23.6)
Central Venous Catheter (CVC)	12 (10.9)
Eye	11 (10.0)
Other	12 (10.9)

The most common infection was systemic infection or septicemia. A variety of organisms generated these infections (Table 3). *Cytomegalovirus* was the most commonly found organism in routine blood cultures. Examples of organisms in category of "other" in Table 3 include: *gram positive corynebacterium* species; *staphylococcus aureus*; *gamma-hemolytic streptococcus*; *methicillin-resistant staphylococcus aureus* (MRSA); *vancomycin-resistant enterococci* (VRE); and *Escherichia coli* (*E. coli*).

Table 3

Organisms Related to Septicemia ($n = 68$)

	f (%)
Cytomegalovirus (CMV)	47 (42.7)
Coagulase-negative staphylococcus (CNS)	14 (12.7)
Epstein-Barr virus (EBV)	8 (7.3)
Enterococcus	4 (3.6)
Pseudomonas species	3 (2.7)
Gram-negative rods	3 (2.7)
Gram-positive bacilli	3 (2.7)
Gram-positive coccus species	3 (2.7)
Other	7 (6.4)

Urinary tract infections (UTI) were ranked the second most common infection in this study. Female subjects had a higher incidence of UTI ($n = 36$, 32.7%) than male subjects ($n = 21$, 19%). Table 4 displays organisms related to UTI. Results from cytology indicated BK virus was the leading cause of UTI among allogeneic BMT recipients in this study. Organisms listed in category "other" in Table 4 are: CMV; yeast; *staphylococcus* species; *Human Herpes virus Six* (HHV-6); *hemolytic streptococcus*; *necrotizing fasciitis* (NF); *gram- positive coccus* species; and *gram-negative rods* antibiotics resistance (GNRS).

Table 4

Organisms Related to UTI

	f (%)
BK virus	34 (30.9)
Enterococcus species	18 (16.4)
CNS	9 (8.1)
polyoma virus	9 (8.1)
gram-negative rods	8 (7.3)
E. coli	6 (5.4)
VRE	6 (5.4)
pseudomonas	3 (2.7)
Other	10 (9.1)

Findings

Research Question 1

To answer the first research question, 'What are the patterns of weight recovery and serum albumin levels among post-allogeneic BMT recipients during the 100 days post-BMT?' two advanced practice nurses (APN) and one registered dietitian routinely involved with in post-BMT care were selected to sort the Excel graphs of weight recovery and serum albumin levels. Raters were not given a set of criteria to use for the sorting task and each used different criteria to sort the graphs into categories. The categories identified were highly divergent with graphs divided into 4 to 23 categories.

Three raters categorized weight recovery graphs using different criteria (Table 5). The first rater categorized weight graphs into four groups according to overall patterns. Using a more complex schema, the second rater categorized weight graphs into 14 groups focusing the peak and the lowest points of weight changes related to time of transplantation. The third rater categorized weight graphs according to combinations of: (a) trend (erratic, stable, upward, and downward); (b) malnutrition risk (low, moderate, and high); and (c) BMT days, deriving a total of 23 groups:

The same raters categorized serum albumin recovery graphs into groups using similar criteria in weight recovery graphs (Table 6). The first rater sorted albumin graphs into four groups according to general patterns when compared to baseline. The second rater divided the albumin graphs into 12 groups according to the peak and the lowest point of serum albumin related to time of transplantation. The third rater categorized albumin graphs based on: (a) baseline serum albumin (below 2.5, 2.5-3.0, 3.0-3.5, and above 3.5); (b) trend (erratic, stable, upward, and downward); and (c) day of BMT, deriving a total of 22 groups.

In close examination of each graph with subject's study code, the same graph belonged to one subject was placed into different group according to each rater's criteria. There was no conclusive agreement among these findings thus preventing any further analysis.

Table 5

Rater Trends for Weight Patterns
($N = 110$)

Rater and Trends for Weight	*f* (%)
Rater 1	
Trends	
Stable/Predictable	40 (36.4)
Unpredictable/Erratic	36 (32.7)
Upslope Trend	4 (3.6)
Consistent Downslope	30 (27.3)
Rater 2	
Trends	
Curve Plateau	35 (31.8)
Trend Down	18 (16.4)
Lowest Point D21	5 (4.5)
Drop 5-10 kgs in 10 Days then Curve Down Trend	4 (3.6)
Trend Up	3 (2.7)
Weight Down Trend then Peak after D50 then Down Trend	7 (6.4)
Weight Dropped First 10 Days then Plateau	6 (5.4)
Weight Drop more than 10 kgs D10-30 then Down Trend	4 (3.6)
First Peak around D10-20	4 (3.6)
Highest Peak D10-20 then Plateau	6 (5.4)
Highest Peak D10-17 then Down Trend	9 (8.2)
Peak D20-30 then Down	4 (3.6)
Peak D50 then Down Trend	2 (1.8)
Saw-Tooth Trend	2 (1.8)
Plateau then Drop D70	1 (0.9)

(table continues)

Table 5 (continued)

Rater Trends for Weight Patterns
($N = 110$)

Rater and Trends for Weight	*f* (%)
Rater 3	
Trends	
Erratic, Low Risk, D90-100	1 (0.9)
Erratic, Moderate Risk, D70-80	1 (0.9)
Erratic, Moderate Risk, D90-100	16 (14.5)
Erratic, High Risk, D50-60	1 (0.9)
Erratic, High Risk, D90-100	6 (5.4)
Stable, Low Risk, D80-90	2 (1.8)
Stable, Low Risk, D90-100	27 (24.5)
Stable, Moderate Risk, D90-100	5 (4.5)
Upward, Low Risk, D80-90	2 (1.8)
Upward, Moderate Risk, D20-30	2 (1.8)
Upward, Moderate Risk, D80-90	1 (0.9)
Upward, Moderate Risk, D90-100	1 (0.9)
Upward, High Risk, D60-70	3 (2.7)
Downward, Low Risk, D60-70	1 (0.9)
Downward, Low Risk, D70-80	1 (0.9)
Downward, Low Risk, D80-90	1 (0.9)
Downward, Low Risk, D90-100	7 (6.4)
Downward, Moderate Risk, D40-50	1 (0.9)
Downward, Moderate Risk, D70-80	1 (0.9)
Downward, Moderate Risk, D80-90	2 (1.8)
Downward, Moderate Risk, D90-100	15 (13.6)
Downward, High Risk, D40-50	2 (1.8)
Downward, High Risk, D80-90	11 (10.0)

Table 6

Rater Trends for Serum Albumin Patterns
($N = 110$)

Rater and Trends for Albumin Levels	*f* (%)
Rater 1	
Trends	
Erratic Trend	49 (44.5)
Stable Trend	32 (29.1)
Upward Trend	24 (21.8)
Downward Trend	5 (4.5)
Rater 2	
Trends	
Drop D10-20	27 (24.5)
Drop D10 then Rise	7 (6.4)
Drop D30	5 (4.5)
Drop D50	1 (0.9)
Downward Curve	7 (6.4)
Lowest D61-74	2 (1.8)
Upward Trend	6 (5.4)
Trend Up Post D10	19 (17.3)
Rise after D40	2 (1.8)
Peak D20	14 (12.7)
Peak D30	6 (5.4)
Plateau	14 (12.7)

(table continues)

Table 6 (continued)

Rater Trends for Serum Albumin Patterns
($N = 110$)

Rater and Trends Albumin Levels	*f* (%)
Rater 3	
Trends	
Below 2.5, Erratic D90-100	1 (0.9)
2.5-3.0, Erratic D90-100	2 (1.8)
3.0, Erratic D80-90	1 (0.9)
3.0-3.5, Erratic D90-100	6 (5.4)
Above 3.5, Erratic D90-100	8 (7.3)
Below 2.5, Stable D90-100	2 (1.8)
2.5-3.0, Stable D90-100	7 (6.4)
3.0-3.5, Stable D80-90	3 (2.7)
3.0-3.5, Stable D90-100	16 (14.5)
Above 3.5, Stable, D90-100	18 (16.4)
Below 2.5, Upward D90-100	4 (3.6)
2.5-3.0, Upward D90-100	7 (6.4)
3.0-3.5, Upward D60-70	1 (0.9)
3.0-3.5, Upward D80-90	3 (2.7)
3.0-3.5, Upward D90-100	5 (4.5)
Above 3.5, Upward D90-100	9 (8.2)
Below 2.5, Downward D20-30	2 (1.8)
2.5-3.0, Downward D40-50	2 (0.9)
2.5-3.0, Downward D50-60	1 (0.9)
3.0-3.5, Downward D30-40	1 (0.9)
3.0-3.5, Downward D70-80	4 (3.6)
Above 3.5, Downward D90-100	7 (6.4)

Research Question 2

Research question two focused on the relationships between malnutrition indicators (weight loss and hypoalbuminemia) and the outcomes of transplantation (infections and mortality) during the 100 days post-BMT. Fisher's Exact tests were used to determine difference in (a) malnutrition indicated by weight loss and transplant related mortality; and (b) malnutrition indicated by hypoalbuminemia and transplant related mortality. A *t*-test for independent samples was used to compare differences in malnutrition (indicated by weight loss or no weight loss) and transplant related infection. A Kruskal- Wallis one-way analysis of variance determined differences in malnutrition as assessed by high risk, moderate risk, and low risk hypoalbuminemia levels and transplant related infection.

There were ten incidences of mortality reported among 110 subjects during the first 100 days post-BMT. To determine the differences of transplant related mortality i.e. those who survived versus did not survive among two groups of subjects with malnutrition, subjects were divided into two groups according to their weight loss. Subjects who lost more than 5% or more from baseline within 30 days or 7.5% within 90 days were categorized as malnourished (68 subjects, 61.8%). The remaining 42 (38.2%) were placed in the nonmalnourished group. A Fisher's Exact probability test indicated no significant relationship between malnutrition and transplant related mortality among allogeneic-BMT recipients during 100 day post BMT ($p = .186$).

Subjects were categorized into 3 groups based on their serum albumin level to compare the differences of transplant related mortality among subjects with malnutrition

indicated by hypoalbuminemia. There were 44 (41.1%) in the high risk group, 44 (41.1%) in moderate risk and 19 (17.7%) in the low risk group. Only one subject who died had moderate risk of hypoalbuminemia and there were no deaths in low risk group. Therefore moderate risk and low risk categories were collapsed. Nine of the ten subjects who died within 100 days post BMT were categorized in high risk group. A Fisher's exact probability test was statistically significant finding, (p = .001) indicating that high risk patients with low albumin levels had a greater incidence of mortality.

A two tailed t-test for independent samples was used to assess the differences in transplant related infection between two groups of subjects classified as either having or not having malnutrition. A significant difference was noted, $t(108) = -4.02$, $p < .0005$. Infection incidences were higher among malnourished group ($M = 5.35$, $SD = 3.26$) than non-malnourished group ($M = 2.86$, $SD = 2.99$).

To determine the differences of transplant related infection incidences among three risk groups (indicated by hypoalbuminemia), a Kruskal-Wallis one-way analysis of variance by ranks (KW Test), a nonparametric test, was used in place of one-way independent sample of ANOVA because of the lack of homogeneity of variance. The three subjects who had normal serum albumin during 100 days post BMT were dropped from this analysis.

The outcome of KW test indicated a significant difference of infection incidences among three risk groups, $\chi^2 = 32.489$ ($df = 2$, $N = 107$), $p < .0005$. Subjects with lower serum albumin level had higher incidence of infections: (a) high risk group (287

incidences); (b) moderate risk group (156 incidences); and (c) low risk group (35 incidences).

Three pairwise post hoc comparisons of the groups were done and revealed significant differences between high risk versus the moderate risk group and the high risk group versus low risk group. The differences were not significant between the moderate group versus low risk group. The high risk group experienced significantly more infections than the moderate risk group and the low risk group. In addition to this, the significant findings from KW test and the post-hoc comparison between the three risk groups (hypoalbuminemia) suggested that the incidence of infection increased significantly when serum albumin dropped below 3 gm/dL (moderate risk) and 2.5 gm/dL (high risk) respectively.

Research Question 3

The third research question asked 'Do allogeneic BMT recipients with a low body mass index (underweight or normal weight) prior to BMT have a higher incidence of transplantation-related mortality rate than allogeneic BMT recipients with high body mass index (overweight or obese) during the 100 days post-BMT?'. To compare transplant related mortality between the group with low BMI versus the high BMI group, subjects were categorized based on their pre-transplant baseline BMI into 4 groups using the Centers for Disease Control and Prevention (CDC) BMI classification: (a) underweight group (none); (b) normal weight group (n = 34, 30.9%); (c) overweight group (n = 40, 36.4%); and (d) obese group (n = 36, 32.7%). From this categorization, groupings were combined into two groups: the normal/underweight group and the

overweight/obese group. In the normal weight group there were two (1.8%) deaths and in the overweight /obese group there were eight (7.3%) deaths post BMT. Because only two subjects who had normal weight died during 100 days post BMT, a Fisher's Exact Test for two independent samples (2x2) was used and revealed no significant differences in mortality and BMI among allogeneic-BMT recipients during 100 days post BMT (p = .325).

Research Question 4

The fourth research question examined degree of mucositis and its relationship to infection post BMT. To answer research question four, subjects were divided into two groups based on the severity levels of mucositis during BMT. All subjects in this study experienced mucositis with different levels of severity based on WHO mucositis classification, grade I (n = 4, 3.6%); grade II (n = 27, 24.5%); grade III (n = 59, 53.6%), and grade IV (n = 20, 18.2%). Subjects experiencing grade I and II mucositis were categorized to the mild group and grade III/IV were in the severe group. A total of 31 (28.2%) patients were in the mild mucositis category and 79 (71.8%) fell into the moderate/severe category. A two tailed t-test for independent samples was used to determine differences in transplant related infection between subjects with mild versus severe mucositis.

Infection incidence was slightly higher among grade III/IV mucositis group (M = 4.49, SD = 3.13) than grade I/II group (M = 4.16, SD = 3.97). However, the differences were not significant, $t(108) = -.463$, $p = .64$.

Research Question 5

Research question five examined the predictive ability of lowest BMI and lowest serum albumin levels during the first 30 days post BMT for infection during first 100 days post BMT when controlling for the variables age of recipient, time of transplant, and development of acute GVHD or relapse in 100 days. A hierarchical regression model was used to determine if malnutrition indicators of lowest BMI and lowest serum albumin during the first 30 days were significant predictors of infection for first 100 days post BMT. A block of independent variables including age, time of transplant, acute graft-versus-host disease, and relapse was entered into the analysis first as control variables then the malnutrition indicators were entered.

Bivariate scatterplots failed to show any linear or curvilinear relationships. The normal probability plot of the residuals appeared to be a straight line. Scatterplot of the residuals appeared evenly distributed in both upper and lower values around the line, no curvilinear relationship, no detached value. Homoscedasticity, independence and normality assumptions were met.

The result of this analysis showed that malnutrition indicators of lowest BMI and lowest serum albumin level are significant predictors when age, time of transplant, acute GVHD, and relapse are controlled, R^2 change = .147, F change (2, 103) = 9.188, $p <$ .0005. The beta weight for serum albumin (-.369) is bigger than the beta weight for BMI (.134). Therefore, serum albumin is considered a stronger predictor than BMI.

Research Question 6

Research question six examined the predictive ability of lowest BMI, and lowest serum albumin levels during the first 30 days post BMI for mortality during one year post BMT when controlling for the variables age of recipients, time of transplant, development of chronic Graft versus Host Disease (GVHD), and relapse. A logistic regression was used for analysis. Among 100 subjects who survived the first100 days post BMT, 26 subjects died within one year post BMT. Independent variables were BMI for first 30 days, serum albumin levels for first 30 days, age, time of transplant, presence of acute GVHD, and relapse.

Standardized residuals were screened for outliers in order to meet the assumptions of logistic regression (Garson, 2010). Five subjects showed standardized residuals greater than 2.58 indicating outliers at the .01 level. Outliers – consisting of five subjects- were removed before proceeding with further analysis.

Data for the five subjects composing the outlier group was reviewed. All 5 subjects died within one year post BMT and experienced chronic GVHD. There is possibility that other crucial variables occurring between Day 100 to one year were omitted from this analysis because of lack of specification in this model. The intense of chart review in this study stopped at 100 days post BMT. An extensive review of information after Day 100 to one year would be necessary to gather the information needed. Logistic regression was not done due to lack of information as indicated by standardized residuals as outliers.

Summary of the Findings

While all subjects in this study were in or above normal weight category before receiving BMT, two-third of subjects experienced weight loss and almost all subjects had hypoalbuminemia indicating malnutrition after BMT. While weight loss was not related to transplant mortality, it significantly contributed to an increase in transplant related infection. Hypoalbuminemia was significantly related to both transplant related mortality and infection especially when serum albumin dropped below 3 gm/dL. Body mass index was not related to transplant related mortality during 100 days post BMT. Although the majority of subjects experienced mucositis to the point that it interfered their eating and swallowing solid food, severity in mucositis did not contribute to transplant related infection. Both BMI and hypoalbuminemia were significant predictors of transplant related infection during 100 days post BMT. Predictors for transplant related mortality in one year have not been identified. For the first research question, there was no conclusive agreement among three raters in identifying the patterns of weight recovery and of serum albumin levels among 110 post-allogeneic BMT recipients during the 100 days post-BMT.

CHAPTER V

SUMMARY OF THE STUDY

The purpose of this study was to identify complications related to blood and marrow transplantation (BMT) process, the presence of malnutrition among patients who received myeloablative allogeneic BMT, and the predictive effects of malnutrition indicators to the outcomes of BMT. Six research questions related to malnutrition were investigated: (a) weight and albumin recovery patterns; (b) malnutrition indicators and outcomes of BMT; (c) body mass index (BMI) and incidences of transplant related mortality; (d) degree of mucositis and its relationship to transplant related infections; (e) predictive ability of BMI and serum albumin levels and infection incidences; and (f) predictive ability of BMI and serum albumin levels and mortality incidences during the first year post BMT. This chapter summarizes the findings of the study, provides a discussion of findings in relation to current literature, presents conclusions and implications, and offers recommendations for future research.

Summary

A retrospective chart review from 110 electronic medical records of patients diagnosed with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS), who received the same regimen of myeloablative, allogeneic BMT from one cancer institution during August, 2005 to June, 2008 was conducted. The intensive chart review

focused primarily on information during the first 100 days post BMT although data were also gathered regarding patient status one-year post BMT.

The sample consisted of 110 patients who had undergone allogeneic BMT and had relevant data extracted from their medical records. Males composed slight more than half of the sample. Acute myeloid leukemia (AML) was the most common diagnosis with approximately one-fourth of donors diagnosed as having myelodysplastic syndrome (MDS). The sample was primarily Caucasian with small representations from Hispanics and African Americans.

Discussion of the Findings

All subjects in this study received myeloablative allogeneic BMT which is associated with gastrointestinal toxicity, prolonged impaired immunological function, and higher incidence of infections. To assess the impact of these factors, two indicators of malnutrition – body mass index (BMI) and albumin levels were studied in relation to transplant related infections and mortality. Additionally mucositis was examined because of its potential impact on nutritional status of BMT patients. Findings from this study suggested a high incidence of mucositis, malnutrition, and infections among these subjects which is congruent with previous studies documenting that BMT recipients experienced eating difficulties 66% (Iestra et al., 2002) and weight loss 28% (Lenssen et al., 1990). Results of the current study suggest that most subjects experienced eating difficulties (71.8%) and weight loss (99%). The average weight loss was 8.39 kgs and 68 subjects (61.8%) in this study were categorized as having severe weight loss (malnutrition). Overall survival after 100 days and one year post BMT were 91% (n =

100) and 67.3% (n = 74), respectively. This discussion examines malnutrition and infection, malnutrition and mortality, and mucositis and infection.

Malnutrition and Infection

Infection is a significant concern for BMT patients. Consequently, all subjects in this study received multiple antimicrobial prophylaxis therapies during the first 100-days post BMT with regular surveillance cultures for early diagnosis of any asymptomatic infections. In spite of preventive therapy, over 91% of subjects (n = 101) in this study experienced at least one episode of infection.

Over 60% of subjects had systematic infections most often caused by *cytomegalovirus* (CMV). Although not often reported in the literature as a transplant related infection, over half of subjects experienced urinary tract infections (UTI), ranking as the second most common infection in this study. While UTI was not considered a life-threatening condition, the pain related to bladder spasm while passing blood clots through the urethra were severe and required pain management or admission for bladder irrigation with aggressive intravenous hydration and antimicrobial therapies.

Although central venous catheter (CVC)-related septicemia incidences were previously reported as high as 45%,(Elishoov et al., 1998), the current study found much lower incidence of catheter-related infection, 12 subjects (10.9%). One reason for the lower infection rate may be stringent protocols used for catheter care by the participating institution. A variety of organisms including *gram –negative bacteria* related septicemia (52%), *gram-positive bacteria* related septicemia (42%), and *candida species* septicemia (5%) have been reported as causative agents (Elishoov et al., 1998). In this study, there

were 13 organisms found among 15 episodes of CVC-related infection including eight *gram-positive bacteria* (61.5%) organisms, two *gram-negative bacteria* (15.3%), and two fungal infections (n = 15.3%).

Fewer than 50% of subjects in this study were diagnosed with respiratory tract infections that included pneumonia; sinusitis; and upper respiratory infection. Previous study reported that respiratory syncytial virus (RSV) and parainfluenza type 3 were seasonal infection among patients with hematologic malignancies and BMT recipients and the incidences were 31% and 23%, respectively (Chemaly et al., 2006). Microbiology reports from subjects in current study indicated that RSV (n = 3, 2.7%) and parainfluenza type 3 infections (n = 5, 4.5%) were much lower incidences.

The possible reasons why this study had a lower incidence of RSV was the differences of sample characteristics. Subjects in Chemaly et al.' study were more diverse in diagnosis and treatment including: (a) all types of BMT (autologous and allogeneic BMT); (b) older subjects (over 65 years); (c) non-BMT recipients (leukemias; lymphoma, myeloma, and Hodgkin disease); and (d) focusing only viral respiratory tract infections.

Defining infection in this study proved difficult. Originally, infection incidence was defined according to positive results of microbiology cultures. However, documentation related to infection diagnoses and treatments among subjects in this study required a broader scope of definition. Many incidences of infection were diagnosed without positive results of cultures, but rather were based on clinical signs and symptoms or radiographic studies. These included infections such as oral thrush, tooth decay, gum abscess, groin abscess, ingrown toe nails, appendicitis, cholecystitis, pneumonia, and

sinusitis. Another issue was that many patients had positive results from blood cultures with the same organism for a long period of time extending beyond 2 weeks. In other cases, the same site was infected with different organisms such as cystitis or urinary tract infection (UTI). Or, conversely, the same organism caused infections in multiple sites on the same host such as herpes virus found on both lips and eyes or yeasts infection that consisted of oral thrush and central venous catheter involvement.

The most significant findings of this study are that malnutrition plays a role in the incidence of transplant related infection. Specifically, low albumin levels are associated with risk of infection. The high risk group with low albumin levels were more likely to have infections that the moderate or low risk groups. Additionally, the malnutrition indicators of low body mass index and low serum albumin levels are predictive of infection when holding constant the factors of age, time of transplant, acute graft-versus-host disease, and relapse. In relation to the theoretical model proposed by Costa (1977), low albumin levels and low body mass index are signs of host depletion that predisposes individuals to decreased immunocompetence. The increased infection rate of subjects with low serum albumin and low BMI are congruent with this model.

Malnutrition and Mortality

Another major finding of this study was that patients with severe hypoalbuminemia were significantly more likely to die than post BMT patients with higher albumin levels. Nine of ten subjects (8% of total subjects) who died during 100 days post BMT had severe hypoalbuminemia. Eight of ten subjects (7.3% of total subjects) who died in this study were also categorized as having severe weight loss

(malnutrition). Mortality related to malnutrition (hypoalbuminemia and weight loss) in this study was much lower than Zacharakis et al.' study 18.7% and 38.3%, respectively.

Some reasons for the lower mortality is that this study was conducted for a shorter period (100 days) post BMT when compared to two-year period in Zacharakis et al.' study. Additionally, there may be differences in samples including host depletion extending over a longer period of time, type of cancer diagnosis, and differences in staging of the cancer.

Mucositis and Infection

In this study, all patients experienced mucositis with over 70% experiencing severe mucositis rated as level 3 or level 4. Subjects began developing mucositis during the first 14 days post BMT. This finding is congruent with other studies regarding BMT patients. Incidence of reported oral mucositis ranged from 88% to 99% (Sonis et al., 2001; Wardley et al., 2000), starting from 4-5 days post BMT and lasting up to 3 weeks (Sonis et al., 2001). Although, Palifermin had been reported in reducing the severity and duration of mucositis (Spielberger et al., 2005), during chart review it was noted that no patients had Palifermin prescribed.

Approximately 15% of subjects experienced oral candidiasis in this study. This incidence is far lower than those of Einsele et al.(2003) who reported oral *candida* colonization was greater than 60%. The reasons for the lower infection rate can be related to institutional precautions and policies for regular oral assessment, monitoring, and mouth care. Also, mucositis occurred during the first 30 days post BMT while subjects

were usually admitted in the hospital receiving intense systemic antibiotics. These may have prevented a greater incidence.

Conclusions

Conclusions of the study are:

1. Severe hypoalbuminemia is an indicator of the potential for mortality in post BMT patients.
2. Low albumin levels are associated with an increased risk for infection following BMT.
3. The malnutrition indicators of low body mass index and low serum albumin levels are predictive of infection when holding constant the factors of age, time of transplant, acute graft-versus-host disease, and relapse.
4. Serum albumin is a stronger indicator for infection potential in post-BMT patients.

Findings from this study suggested that malnutrition was a common occurrence among post BMT recipients. Specific indicators of poor nutritional status that are associated with an increase of infections are low BMI and hypoalbuminemia. Additionally, very low albumin levels were associated with mortality.

Implications

Body weight and serum albumin are good nutritional assessment tools. According to Blackburn, Bistrain, Maini, Schlamm, and Smith (1977), the best nutrition assessment tool is the indicator which can reflect the presence of malnutrition, assess its severity, and be used as periodic measurement to evaluate the effectiveness of nutrition therapy. Based

on Blackburn's et al. recommendations and the study findings, the following measures are proposed:

1. measurement of weight and serum albumin level at each clinical visit should be routinely done
2. a comprehensive nutritional profile including line graphs of weight recovery and serum albumin levels should be completed for each patient. If weight falls by more than 5% from the baseline weight or albumin levels fall below 3 gm/dL, health care professionals should refer patients for nutritional consultation.
3. clinicians should attend to co-existing medical problems such as those found with adults having cardiopulmonary problems that may present at clinic visits with weight gain – allowing their malnourished condition to be missed if clinicians use weight loss as guideline alone.

Almost all of the subjects in this study experienced mucositis lasting up to 27 days which interferred patients' ability to eat and swallow. In clinical practice the issue of malnutrition should be proactively addressed. These practices should include:

1. education sessions for patients and families prior to BMT emphasizing the importance of oral intake - particularly protein intake during the post BMT period
2. arrange for dietician consultation with individual patients to discuss his/her daily requirement of caloric intake before BMT
3. post BMT, clinicians should assess the daily weight and compare it to admission weight to detect early signs of malnutrition

4. post BMT, clinicians should routinely check patients for serum albumin levels of 3 gm/dL or less, and monitor patients for signs of infection.
5. post-BMT dietitians should monitor 3-day food records for calorie counts and assess the need for nutritional supplementation
6. Care providers should use infection precautions to prevent potential transmission of hospital acquired infections.

Recommendations for Further Study

Suggestions for future research include:

1. Examine patterns of weight recovery and serum albumin level by developing line graphs of the patterns for each patient in order to develop standardized guidelines for the diagnosis of malnutrition. In this process experts would receive instructions on line graph interpretation and pattern specification to guide sorting. Weight line graphs should be enhanced by adding horizontal lines indicating 5% and 7.5% of admission weight to the weight recovery graphs. Albumin line graphs should be enhanced by horizontal lines indicating the level of 3.5, 3.0, and 2.5 to the albumin graphs to guide clinician in diagnosis of malnutrition.
2. Conduct a protein oral supplement nutritional intervention among hypoalbuminemic post BMT recipients using a prospective, randomized, controlled, pilot study, in order to examine the beneficial effects on BMT outcomes (a) changes in serum albumin levels; (b) incidences of infection; and (c) incidence of mortality.
3. Conduct an intensive chart review from day 100 to one-year post BMT to examine (a) factors that prevent patients returning for regular visit; (b) how local health care

providers communicate and manage long-term post BMT complications; (c) other factors beyond nutritional indicators including incidences of chronic GVHD and relapse; and (d) benefits of monthly visits between 100 days till one year post BMT in terms of early diagnosis and management of chronic GVHD or relapse.

4. Examine the incidence of post transplant infection using a definition of infection incidence that considers (a) site of infection; (b) duration of infection that accounts for infections lasting for an extensive time period (c) invasive (contagious) effects of each organism; (d) treatment options; and (e) methods used to confirm the diagnosis.

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APPENDIX A

Approval Letter from IRB at Affiliated Institution

From: Vera J. DeLaCruz [vjdelacr@mdanderson.org]
Sent: Thursday, December 10, 2009 9:30 AM
To: Popat,Uday R; Lecagoonporn,Srisuda; Quezada,Wanda A; Thompson,Evanna
Subject: Protocol DR09-0774 - IRB Approved

Institutional Review Board (IRB)
Unit 1437
Phone 713-792-2933
Fax 713-794-4589

Office of Protocol Research

To: Uday Popat 12/10/2009
From: Vera J. DeLaCruz
CC: Srisuda Lecagoonporn, Uday Popat, Wanda A. Quezada, Evanna L. Thompson
MDACC Protocol ID #: DR09-0774
Protocol Title: Predictive Effects of Malnutrition Indicators to Morbidity and Mortality Outcomes among Post-
Allogeneic Blood and Marrow Transplantation Recipients
Version: 00

Subject: Protocol DR09-0774 - IRB Approved
Official IRB Approval Date: 12/09/2009
Official IRB Activation Date: 12/10/2009

On 12/09/2009, the Institutional Review Board 4 committee, chair or designee administratively approved the above named and numbered protocol.

It was noted that the protocol, informed consent documents (ICDs) and/or the Waivers of ICD and Authorization are satisfactory and in compliance with federal and institutional guidelines. It was also noted that risks to human subjects are minimal and that confidentiality of records will be maintained. This study has been activated and is now ready for participant accrual.

In keeping with the requirements outlined in 45CFR46.109(e) and 21 CFR56.109(f), the IRB shall conduct continuing review of all protocols at intervals appropriate to the degree of risk, but not less than once per year.

- Waivers of Informed Consent and Authorization have been granted.

Please Note: If a grant is the basis of your protocol, the grant should be funded before research can begin.

In the event of any questions or concerns, please contact the sender of this message at (713) 792-2933.

Vera J. DeLaCruz 12/10/2009 09:29:46 AM

This is a representation of an electronic record that was signed electronically and below is the manifestation of that electronic signature:

Vera J. DeLaCruz
12/10/2009 09:29:15 AM
IRB 4 Chair Designee
FWA #: 00000363
OHRP IRB Registration Number: IRB 4 IRB00005015

APPENDIX B

Approval Letter from IRB at TWU

TEXAS WOMAN'S UNIVERSITY
DENTON DALLAS HOUSTON

The Graduate School
P.O. Box 425649, Denton, TX 76204-5649
940-898-3415 FAX 940-898-3412

0013231

January 12, 2010

Srisuda Lecagoonporn
3016 Holly Hall
Houston, TX 77054

Dear Ms. Lecagoonporn:

I have received and approved the prospectus entitled ***Predictive Effect of Malnutrition Indicators to Morbidity and Mortality Outcomes among Post-Allogeneic Blood and Marrow Transplantation Recipients*** for your Dissertation research project.

Best wishes to you in the research and writing of your project.

Sincerely yours,

Ruth A. Johnson, Ph.D.
Associate Dean of the Graduate School

cc: Dr. Anne Young, School of Nursing, Houston
Dr. Karen Lyon, Associate Dean, School of Nursing, Houston

APPENDIX C

Data Collection Sheets

Subject ID _____

Demographic Information

Date of Birth	DD/MM/YY	
Gender	M/F	
Ethnicity (if known)		
Occupation		
Marital Status (# of children)		
Address	City/State	
Diagnosis (FAB classification)	AML/MDS	
Date of Diagnosis	MM/YY	
Age at Dx	## years	
Blood Type		
Known Diseases	Y/N	
Tobacco Use	Y/N	
Alcohol Use	Y/N	
Drug Use	Y/N	

Transplantation Information

Allo-BMT Type	Related/MUD	
In-pt admit Date	DD/MM/YY	
Transplant Date (Day 0)	DD/MM/YY	
Age at Transplant	#years	
D/C from In-pt Date	DD/MM/YY	
Length of Stay	## days	
Out-pt starting Date	DD/MM/YY	
Date of Engraftment	DD/MM/YY(Day)	

Subject ID _____

Donor Information

Related to Pt	Y/N	
Relationship to Pt	Sibling/children	
Gender of Donor	M/F	
Marrital status (Female Donor)	Married/single	
Female child bearing	## of children	
HLA matching	(%)	
Donor Age	## years	
Blood Type		
Health History		

In-Patient Complications

Mucositis	Y/N	
Severity of Mucositis	WHO grade (0-4)	
Duration of Mucositis	## days	
GVHD	Skin/GI/Liver	

Other Complications

Date	Symptoms	Tests	Treatments

Subject ID _____

Out-pt Complications during 100 days

Infection Incidences

Date	Symptoms	Sources of Cultures	CXR/CT scan y/n	Pathogens	Admit y/n	Treatments

Other Complications

Date	Symptoms	Admission Y/N	Treatments

Acute GVHD Incidences

Date	Skin (type of rash, % of body surface)	GI (amount of diarrhea/day)	Liver (Billirubin Level)	Admit y/n	Treatments

Subject ID _____

Chronic GVHD Incidences (after Day 100)

Date	Skin (type of rash, % of body surface)	GI (amount of diarrhea/day)	Liver (Billirubin Level)	Admit y/n	Treatments

Survivorship Information

Last follow-up at MDACC	DD/MM/YY	
Remission (no complications)	Y/N	
Relapse	Y/N (DD/MM/YY)	
Deceased	Y/N (DD/MM/YY)	
Other Cancer	Y/N (DD/MM/YY)	
Cause of Death (if known)		

Nutrition Assessment Information

Height	(meters)	
Weight (Day 0)	(Kgs)	
Usual Wt (if known)	(Kgs)	
Ideal Body Weight (IBW)	(Kgs)	
Body Mass Index (BMI) Day 0		
Lowest Body Wt in 100 days	(Kgs)	
Total wt loss in 100 days	(Kgs)	