STATEMENT BY AUTHOR

This project has been submitted in partial fulfillment of requirements for an advanced degree at The University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this project are allowable without special permission, provided that accurate acknowledgment of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: Lisa Hanna

APPROVAL BY MASTER’S PROJECT DIRECTOR

This Master’s Project has been approved on the date shown below:

Karen Greco PhD, RN, ANP-BC
Date: 
Chair
ACKNOWLEDGMENTS

I would like to express my appreciation to Dr. Karen Greco, RN, ANP-BC, my Master’s degree Project Chair and Dr. Barbara F. Piper, RN, AOCN, FAAN, Co-Chair for their patience, support and guidance throughout this process. Without their leadership and direction this paper would never have been completed.

Many thanks also go to my colleagues at USC Norris and in the division of Hematology, particularly Annette, Linda, Tanya, Pamela, Lisa, Dr Douer, Dr Mohrbacher and Dr Yang, all of whom have been so supportive and a wonderful sounding board in the completion of this project.

Thanks also go to my new best friends, Karla, Megan and Mike. We found each other the first day of this amazing journey and have been glued at the hip ever since. Thank you for all your love and encouragement.

Thank you to my Mum and Dad. Although you are both very far away the love and support you have given me my entire life has helped me tremendously these past few years. I love you and miss you both very much.

Thank you to my wonderful husband, Tarek. You have been my rock for many years now but never more so in the past 2 years. I could never have completed this work without your love, encouragement and support. I love, love.
DEDICATION

This Master’s Project is dedicated to Violet and all those who fight through the complications and long-term treatment required of a diagnosis of Acute Myelogenous Leukemia (AML), Acute Lymphoblastic Leukemia (ALL) or Myelodysplastic Syndromes (MDS).
TABLE OF CONTENTS

LIST OF TABLES ............................................................................................................ 8
ABSTRACT .................................................................................................................... 9

CHAPTER 1: INTRODUCTION .................................................................................. 10

INTRODUCTION ........................................................................................................... 10
BACKGROUND AND SIGNIFICANCE OF PROBLEM ................................................... 11
PURPOSE ..................................................................................................................... 12
SPECIFIC AIMS ............................................................................................................. 12
DEFINITIONS ............................................................................................................... 13
   Acute Myeloid Leukemia (AML) .............................................................................. 13
   Acute Lymphoblastic Leukemia (ALL) .................................................................. 13
   Myelodysplastic Syndromes (MDS) ..................................................................... 14
   Induction Chemotherapy ....................................................................................... 14
   Consolidation Chemotherapy ............................................................................... 14
   Maintenance Chemotherapy ............................................................................... 15
   Salvage Therapy .................................................................................................. 15
   Hematopoietic Progenitor Stem Cell Transplant .................................................. 15
NEUTROPENIA .......................................................................................................... 16
   Short-term ............................................................................................................. 16
   Prolonged ............................................................................................................. 17
   Chronic ................................................................................................................ 17
   Febrile .................................................................................................................. 17
ADVANCED PRACTICE REGISTERED NURSE (APRN) .................................................. 17
HEALTH-RELATED QUALITY OF LIFE (HR-QOL) .................................................... 18
SIGNIFICANCE TO NURSING PRACTICE .................................................................. 19
# TABLE OF CONTENTS - Continued

## RELATIONSHIP OF THIS REVIEW OF THE LITERATURE TO THE SCHOLARLY INQUIRY PROJECT

Project ........................................................................................................................................... 19

Summary ....................................................................................................................................... 20

## CHAPTER 2: REVIEW OF THE LITERATURE .............................................................................. 21

Review of Literature .................................................................................................................. 21

Literature Search Methods ........................................................................................................ 21

Key Words .................................................................................................................................. 21

Databases .................................................................................................................................. 22

Recent Research ....................................................................................................................... 23

Hematological Malignancies ....................................................................................................... 25

Incidence and Prevalence ......................................................................................................... 25

Pathophysiology of Acute Leukemia and Myelodysplastic Syndromes .................................... 26

Disease Presentation and Diagnosis ....................................................................................... 26

Treatment Protocols and their Requirements ......................................................................... 27

Neutropenia and Health-Related Quality of Life ................................................................... 30

Health-Related Quality of Life in Neutropenia Patients ......................................................... 31

Health-Related Quality of Life in Patients with Leukemia or Myelodysplastic Syndromes ..... 36

Measurement of Health-Related Quality of Life .................................................................. 38

Summary ................................................................................................................................... 38

## CHAPTER 3: DISCUSSION .......................................................................................................... 40

Introduction ............................................................................................................................... 40

Clinical Implications for Nursing ............................................................................................ 40
# TABLE OF CONTENTS - Continued

- Advanced Practice Registered Nurse Role in Promoting Health-Related Quality of Life .......................................................... 41
- Nursing and Neutropenia .................................................................................................................................................. 42
- Project Limitations ......................................................................................................................................................... 43
- Recommendations for Future Study .......................................................................................................................... 43
- Conclusions ................................................................................................................................................................. 43

- Appendix A: French, American, British (FAB) Classification of AML ................................................................. 44
- Appendix B: French, American, British (FAB) Classification of ALL ............................................................... 45
- Appendix C: MDS Types and Survival Rates in Years ............................................................................................... 46
- Appendix D: Berlin, Frankfurt, Munster (BFM) Protocol .......................................................................................... 47
- References .................................................................................................................................................................... 48
LIST OF TABLES

TABLE 1: SEARCH KEY WORDS ..................................................................................... 22
TABLE 2: DATABASES SEARCHED ................................................................................. 23
ABSTRACT

Multiple studies over the past 30 years have demonstrated that a person’s health-related-quality of life (HR-QOL) is adversely affected by a diagnosis of cancer, its treatment and treatment-related side-effects such as neutropenia. Despite this fact, no studies have been conducted in adult patients that address the impact that the length, duration, requirements of treatment and neutropenic episodes have on HR-QOL in adults diagnosed and treated for Acute Myelogenous Leukemia, Acute Lymphoblastic Leukemia or Myelodysplastic Syndromes.

This paper documents the pathophysiology of these specific hematologic malignancies, their risk factors, their treatment regimens, types and durations, neutropenia definitions, risk factors and duration, HR-QOL measures, and the role(s) an APRN can play in mitigating the negative consequences of these complex and lengthy treatment regimens and associated prolonged neutropenic episodes may have on these patients’ HR-QOL. This review will highlight not only the need for future HR-QOL research to be conducted in these patients but also will highlight the need to study the unique role(s) that the APRN can play in the promotion of HR-QOL in these patients. This Master’s project serves as the foundation for the Scholarly Inquiry Project that will be completed to partially fulfill the requirements for the Doctor of Nursing Practice degree.
Cancer is a devastating disease that can negatively affect a patient’s health-related quality of life (HR-QOL) (Padilla & Ropka, 2005; Fortner et al, 2004; Crighton, 2004). Treatment for hematologic malignancies in particular, frequently involves complex, intense, and prolonged chemotherapy regimens.

A chemotherapy regimen is considered to be complex and prolonged when it includes many different agents given alone and/or in combination repeatedly over a prolonged period time. These regimens are intense because dosage reduction is seldom considered. The primary treatment outcome is to eradicate and maintain the eradication of all abnormal cells in the bone marrow. This is done despite the known risks associated with these regimens over extended periods of time for the development of anemia, neutropenia, and thrombocytopenia and their associated side-effects (e.g., fatigue, infection, and bleeding). As a consequence, these regimens often require patients to undergo frequent inpatient stays and daily and/or prolonged clinic visits for blood draws, transfusions, and treatments (Fortner et al, 2004; Nirenberg et al 2004; Redaelli et al, 2003). These treatment requirements and their associated side-effects can adversely affect all aspects of a patient’s HR-QOL including usual functioning (e.g., physical, emotional, social, and spiritual), activities of daily living and participation in activities that give meaning and value to a person’s life. Despite this fact, little is known about how HR-QOL is affected in these patients.
Background and Significance of the Problem

While relatively rare, hematological malignancies in adults are becoming increasingly more common as the population ages. Despite the significant advances being made in treatment methods and improved survival rates in patients with hematological malignancies, many of these patients unfortunately still cannot be cured (Dombret, Raffoux and Gardin, 2008; Bloomfield et al, 2008). Those who do survive the immediate side-effects of treatment and who go on to experience prolonged remissions following induction and consolidation phases of treatment, must often continue to live with decreased functioning and decreased HR-QOL over time as they continue to deal with the multifaceted challenges of living with the uncertainty associated with the risk of disease recurrence and the symptom burden associated with ongoing maintenance or chronic therapies (Efficace et al, 2007).

Thirty years ago Burge et al (1975) stated that “…quality of life in leukemia [a form of hematological malignancy] is as important as its quantity”. Further recognition of the importance of HR-QOL and its measurement in cancer patients comes from the Food and Drug Administration (FDA) (1985) when this agency supported using HR-QOL assessments as outcome measures in clinical trials of new anti-cancer drugs. Despite the recognition of its importance and the FDA’s recommendations to include HR-QOL outcome measures in cancer drug trials, very few if any Phase I or II clinical trials include HR-QOL as an outcome measure, especially from the patient’s own perspective (e.g., patient reported outcome or PRO) (Efficace et al, 2007). In addition, very few Phase III randomized controlled trials in Hematology include HR-QOL as an outcome measure.
While much has been written about HR-QOL in solid tumor and short-term neutropenic patients (Padilla & Ropka, 2005; Fortner, Houts & Schwartzberg, 2006; Fortner et al, 2005; Ozer, 2003), few if any studies have examined the HR-QOL effects from the patient’s perspective of these complex, prolonged, and intense treatments, their requirements, and associated neutropenia states in hematologic malignancies. In addition, none have investigated the role(s) that an Advance Practice Nurse (APRN) can play in mitigating these negative HR-QOL effects overtime. Thus, the reason for undertaking this review of literature (ROL) for my Master’s Degree Project. This ROL will form the foundation for my future Scholarly Inquiry Project (SIP) that will be conducted in partial fulfillment of requirements for my Doctor of Nursing Practice Degree.

Purpose and Specific Aims

Purpose

The primary purpose of this ROL is to determine what is known about patients with selected hematologic malignancies undergoing complex, prolonged and intense treatment regimens and how the requirements of these regimens and their associated side-effects (e.g., prolonged neutropenia) (Fortner et al, 2004; Nirenberg et al 2004; Redaelli et al, 2003) affect HR-QOL in these patients. A secondary purpose is guide the design and selection of measures used in future research related to HR-QOL in this population.

Specific Aims

In patients with selected hematologic malignancies undergoing intense, prolonged, and complex treatment regimens associated with prolonged neutropenia:
1) Review how disease and treatment-related side-effects such as prolonged neutropenia affect HR-QOL in these patients;

2) Examine how HR-QOL and prolonged neutropenia are conceptualized, defined and measured in these patients, and

3) Review the roles that an APRN can play in mitigating the negative HR-QOL effects of these treatment requirements and associated prolonged neutropenia in these patients.

Definitions

*Acute Myelogenous Leukemia (AML)*

AML is a malignant disorder of the bone marrow in which hematopoietic myeloid progenitor cells stop at an early stage of development, proliferate uncontrollably and cannot differentiate into mature white blood cells (WBCs) (Bloomfield et al, 2008).

*Acute Lymphoblastic Leukemia (ALL)*

ALL is a malignant disorder of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic progenitor cells in the bone marrow (Seiter, 2006). This disorder is differentiated from other lymphoid malignancies by the presence of greater than or equal to 30% lymphoblasts in the peripheral blood or in the bone marrow (which are not normally present) (Lai, Hirsch-Ginsberg & Bueso-Ramos, 2000) as opposed to most lymphomas that originate in the lymphatic system and organs such as the spleen prior to invasion of the bone marrow (Seiter, 2006).
Myelodysplastic Syndromes (MDS)

MDS are a diverse group of hematological conditions united by varying degrees of ineffective production of myeloid blood cells in the bone marrow that have at least a 30% risk of progressing to AML (Strom, Vélez-Bravo & Estey, 2008; Hellström-Lindberg & Malcovati, 2008). There are two variants of MDS, therapy-related (t-MDS) due to prior exposure to cytotoxic therapies and/or radiation therapy and de novo MDS (one that spontaneously develops) (Strom, Vélez-Bravo & Estey, 2008).

Induction Chemotherapy

Induction chemotherapy for each of these three hematological malignancies consists of an initial treatment designed to achieve a complete remission defined as the “…resolution of morphologically detectable disease [in the bone marrow] and restoration of normal blood counts” that has been defined as less than 5% blasts and a hypocellular, regenerating bone marrow on biopsy (Kebriaei, De Lima & Estey, 2008, p. 2235).

Consolidation Chemotherapy

Consolidation chemotherapy in AML, ALL and MDS consists of additional treatment designed to maintain the complete remission achieved by induction chemotherapy treatment, and to eradicate any minimal residual disease to decrease the likelihood of disease relapse (Kebriaei, De Lima & Estey, 2008).
**Maintenance Chemotherapy**

Maintenance chemotherapy consists of lower doses of chemotherapy that while less intense still requires frequent monitoring to evaluate the presence of neutropenia. These therapies are administered to patients with ALL and APL (a subtype of AML) for approximately 2-3 years following induction and consolidation therapies (Kebriaei, De Lima & Estey, 2008). In AML and MDS, research has thus far failed to conclusively determine what the best maintenance therapies for these diseases are. As a consequence, these patients currently do not receive any long-term maintenance treatment (Blum, 2008).

**Salvage Therapy**

Salvage therapy consists of treatment given for disease that either has not gone into a complete remission at the time of induction (primary refractory) or has relapsed post treatment. In patients whose remission has lasted less than one year or in those patients for whom their disease is considered to be refractory, the treatment of choice is an allogeneic hematopoietic progenitor stem cell transplant, preferably in second complete remission (Kebriaei, De Lima & Estey, 2008, 2008).

**Hematopoietic Progenitor Stem Cell Transplantation (HPSCT)**

HPSCT, formerly known as bone marrow transplantation (BMT), involves the intravenous infusion of autologous (self) or allogeneic (donor) stem cells to restore hematopoiesis in patients with damaged or malfunctioning bone marrow (Samaveda, 2007). HPSCT is briefly discussed at various points throughout this ROL as a potential treatment
option. It however is beyond the scope of this paper to evaluate the effects of this particular form of treatment on a patient’s HR-QOL.

Neutropenia

Neutropenia is a decrease in the circulating neutrophil count in the peripheral blood (Godwin, 2008. Its severity is based on the absolute neutrophil count (ANC) (Crighton, 2004). Normally the circulating neutrophil count is 57-67% of the total circulating WBCs in the serum (e.g., approximately 4420 mm$^3$) (Chernecky & Berger, 2004). The ANC is a percentage of the total WBC when a Complete Blood Count (CBC) with differential is ordered. It is calculated by the following formula: $\text{ANC} = \text{total WBC} \times (\% \text{ segmented} + \% \text{ band neutrophils})$ (Kirschbaum, 1998). There are five severity or grading levels for neutropenia as defined by the National Cancer Institute (2003): zero or no neutropenia, one or mild (1500 mm$^3$ to 2000 mm$^3$), two or moderate (1000 mm$^3$ to 1500 mm$^3$), three or severe (500 mm$^3$ to 1000 mm$^3$) and four or profound (less than 500 mm$^3$). Neutropenia can also be defined by its duration, such as short-term, prolonged, and chronic and whether it occurs with a fever (e.g., febrile).

Short-term. Short term neutropenia is defined as a duration of neutropenia lasting less than seven days until recovery of the ANC (greater than or equal to 1500 mm$^3$) following the chemotherapy-induced nadir (defined as the lowest point in the WBC count prior to recovery) (Chen et al, 2003).
**Prolonged.** Prolonged neutropenia is defined as a duration of neutropenia lasting greater than 10 days until recovery of the ANC (greater than or equal to 1500 mm$^3$) following the chemotherapy-induced nadir (Chen et al, 2003).

**Chronic.** Chronic neutropenia is only defined in the arena of congenital neutropenia (an autosomal recessive genetic disorder) where it is classified as an ANC of less than 500 mm$^3$ lasting for more than a few months to years (Boxer, 2006).

**Febrile.** Febrile neutropenia is an oncologic emergency that occurs when a patient develops a fever while being neutropenic with or without any other overt signs or symptoms of infection. Febrile neutropenia mainly occurs due to the myelosuppressive side-effects of most chemotherapies (Kannangara, 2006; Crighton, 2004). Fever within this context is defined as a single temperature of greater than or equal to 38.3°C (101°F) or a temperature of greater than or equal to 38°C (100.4°F) for one hour (Kannangara, 2006).

**Advanced Practice Registered Nurse (APRN)**

Advanced Practice Registered Nurses (APRNs) are RNs who are educationally prepared at the graduate level, have proficiency in an area of clinical specialization and give direct patient care (Cunningham, 2004). The American Association of Colleges of Nursing’s consensus statement (AACN, 2008) defines an APRN as a registered nurse (RN) who has: 1) completed an accredited graduate education program; 2) passed a national certification examination and maintains competency through recertification; 3) acquired advanced clinical knowledge and skills that enable the RN to provide direct care to patients; 4) built on the competencies of RN
practice and shows an increased depth and breadth of knowledge, increased complexity of skills and greater autonomy; 5) become educationally prepared to be accountable for health promotion and maintenance and diagnosis and management of disorders; 6) the clinical experience to show depth and breadth of knowledge; and 7) obtained a license to practice as a certified registered nurse anesthetist (CRNA), clinical nurse specialist (CNS), certified nurse-midwife (CNM) or certified nurse practitioner (CNP). Currently the scope of practice in California (Board of Registered Nursing, 1998) does not require board certification. Certification is required in Arizona (Board of Registered Nursing, 2003).

The AACN (2004) has recommended that the Doctor of Nursing Practice (DNP) be the required graduate degree for all advanced practice nurses and that this recommendation is implemented by 2015. The DNP encompasses seven essential areas of content that include the following: 1) the scientific underpinning for practice; 2) advanced nursing practice; 3) organization and system leadership, quality improvement and system thinking; 4) analytic methodologies related to the evaluation of practice and the application of evidence for practice; 5) utilization of technology and information for the improvement and transformation of healthcare; 6) health policy development, implementation and evaluation; and 7) interdisciplinary collaboration for improving patient and population healthcare outcomes.

**Health-Related Quality of Life (HR-QOL)**

Siddiqui, Kachnic and Movsas (2006) define HR-QOL as something that affects the entire range of a person’s emotions, values and understanding of life. They state that HR-QOL includes general health, physical symptoms, emotional well-being, role and social functions,
sexual functioning, spiritual issues, financial concerns and living conditions. This paper will focus only on the physical and psychosocial aspects of HR-QOL of adult patients with AML, ALL and MDS. Measurement of HR-QOL in these malignancies may be more challenging to study due to the complex, prolonged and complex treatment regimens that may result in many of the very same symptoms that these diseases may cause. In addition, the measurement of HR-QOL may have to be more long-term and be measured longitudinally and repeatedly over time as these patients generally must endure these prolonged treatments and their associated side effects for a longer period of time before any benefit from therapy may be realized (Redaelli et al, 2003).

Significance to Nursing Practice

This Master’s Degree Project (ROL) will advance both the science (knowledge) and practice of nursing as it is one of the first to: 1) review how disease, treatment-related side effects and prolonged neutropenia affect HR-QOL in these patients; 2) examine the conceptualization, definition and measurement of HR-QOL and prolonged neutropenia in these patients, and 3) review the roles that an APRN can play in mitigating the negative HR-QOL effects of these treatment requirements and associated prolonged neutropenia in these patients.

Relationship of this Review of the Literature to the Scholarly Inquiry Project

This ROL creates a more in depth conceptual framework that identifies key components and variables that need to be included in the design of future studies that evaluate HR-QOL in these patients, the role(s) that an APRN can play in this area of practice, and the specific measures that will be used in the SIP.
Summary

HR-QOL in adult patients undergoing treatment for hematologic malignancies has not been well-studied nor have the role(s) that an APRN can play in mitigating the negative HR-QOL effects associated with these complex, prolonged, and intense treatment regimens and the associated prolonged neutropenia in these patients. It is hoped that the results of this ROL and the SIP that follows will lead to the creation of programs that will improve a patient’s HR-QOL through the implementation of an APRN-guided protocol.
CHAPTER 2 – REVIEW OF THE LITERATURE

The primary purpose of this chapter is to review the literature (ROL) to determine what is known about patients with selected hematologic malignancies undergoing complex, prolonged, and intense treatment regimens and how treatment requirements and their associated side-effects (e.g., prolonged neutropenia) (Fortner et al, 2004; Nirenberg et al 2004; Redaelli et al, 2003) negatively affect HR-QOL in these patients. A secondary purpose is to begin to guide the design and selection of measures that will be used in my Scholarly Inquiry Project.

The following key concepts of an emerging conceptual framework are discussed in the following sections of this chapter: 1) incidence, prevalence, and diagnosis of AML, ALL and MDS in adult cancer patients; 2) how disease and treatment-related side-effects such as prolonged neutropenia affect HR-QOL in these patients; and 3) how HR-QOL and neutropenia are measured in these patients. Chapter 3 will focus on addressing the fourth aim of this ROL: 4) what roles an APRN can play in mitigating these negative HR-QOL effects in these patients.

Literature Search Methods

Key Words

A broad search of the literature was initially conducted using the keywords listed in Table 1 and retrieved 369,499 abstracts, articles and presentations. By limiting the search strategy to articles in English, adults over the age 19 and those published in 2003-2008, this initial number was reduced to 39,541. These keywords were then combined to create 70 searchable categories with a final number of 96 evaluable articles and abstracts retrieved.
Table 1

*Search Key Words*

<table>
<thead>
<tr>
<th>General</th>
<th>Expanded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>biphenotypic leukemia, hematologic neoplasms, bone marrow neoplasms</td>
</tr>
<tr>
<td>Leukemia</td>
<td>myeloid, acute or Promyelocytic</td>
</tr>
<tr>
<td>Leukemia</td>
<td>lymphoid, b-cell, t-cell, precursor lymphoblastic, precursor b-cell</td>
</tr>
<tr>
<td></td>
<td>lymphoblastic</td>
</tr>
<tr>
<td>MDS</td>
<td>myelodysplastic/myeloproliferative, refractory anemia</td>
</tr>
<tr>
<td>Advanced Practice</td>
<td>nurse practitioners, nurse clinicians, advanced nursing practice, oncology</td>
</tr>
<tr>
<td></td>
<td>nursing, Oncology Nursing Society, nurse and patient navigation, evidence-</td>
</tr>
<tr>
<td></td>
<td>based practice and medicine, health services accessibility, nurse-patient</td>
</tr>
<tr>
<td></td>
<td>relations, patient education</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>leucopenia, agranulocytosis, lymphopenia, fever, febrile, prolonged</td>
</tr>
<tr>
<td>Growth Factors</td>
<td>granulocyte colony stimulating factors, granulocyte-macrophage colony</td>
</tr>
<tr>
<td></td>
<td>stimulating factor</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>HR-QOL in Cancer, Oncology and/or Hematology, HR-QOL measurement tools</td>
</tr>
</tbody>
</table>

*Databases*

Multiple databases were searched to ensure that all salient articles were retrieved. A general search of Google and Google Scholar was also undertaken. These search strategies were complemented by using author-specific searches and by retrieving articles from the article reference lists. Table 2 lists the databases used in the search strategy.
Table 2

*Databases Searched*

<table>
<thead>
<tr>
<th>Databases</th>
<th>Years Searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Index to Nursing and Allied Health Literature (CINAHL)</td>
<td>1982-2008</td>
</tr>
<tr>
<td>OVID Medline</td>
<td>1996-2008</td>
</tr>
<tr>
<td>Allied and Complementary Medicine (AMED)</td>
<td>1985-2008</td>
</tr>
<tr>
<td>Evidence Based Medicine reviews (Cochrane, DSR, ACP Journal Club, DARE,</td>
<td>1966-2008</td>
</tr>
<tr>
<td>CCTR, HTA, NHSEED)</td>
<td></td>
</tr>
<tr>
<td>OVID Health Star</td>
<td>1966-2008</td>
</tr>
<tr>
<td>Google and Google Scholar</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: Table abbreviations are as follows.

DSR – Data Set Ready
ACP Journal Club – American College of Physicians
DARE - Database of Abstracts of Reviews of Effectiveness (Cochrane Library)
CCTR – Cochrane Controlled Trials Register
HTA – Health Technology Assessment

*Recent Research.*

At the most recent American Society of Hematology (ASH) meeting in December 2008 there were a total of 6,314 abstracts, posters and presentations submitted. Of these, 76 discussed HR-QOL in Hematology patients. Of these, most addressed the short and long term effects of
HPSCT. Only two posters addressed the importance of a patient’s HR-QOL in making treatment
decisions (Oliva, Clissa et al, 2008) and in disease prognosis (Oliva, Latagliata et al, 2008). One
additional poster discussed the psychometric validation of the Functional Assessment of Cancer
Therapy – Neutropenia (FACT-N) scale for measuring HR-QOL in these patients (Lathia et al,
2008). None of the presentations addressed HR-QOL in patients with acute leukemia or MDS
receiving treatment.

Two National Cancer Institute (NCI) funded clinical trials are currently recruiting
participants to evaluate HR-QOL in patients with AML or MDS (National Institutes of Health,
2008). One study is being conducted by an Italian group (Gruppo Italiano Malattie Ematologiche
dell'Adul-to [GIMEMA]) in Italian patients with newly diagnosed MDS. Its stated outcome is to
determine the prognostic effect of pretreatment fatigue on overall survival (Clinicaltrials.gov,
2008). The second trial began in 2004 at the University of Texas M.D. Anderson Cancer Center
in Houston and is anticipated to be completed April 2010. This study is recruiting newly
diagnosed adult patients with AML and MDS. This trial has four purposes: 1) to evaluate the
disease effects of treatment; 2) to determine the effects of treatment on the patient’s ability to
think and perform everyday tasks, 3) to determine the frequency with which these cognitive and
functional effects occur; and 4) to determine these treatment-related cognitive and functional
effects on HR-QOL in these patients (Clinicaltrials.gov, 2008).

In recognition of the absence of studies and guidelines for HR-QOL and the measurement
of symptoms from the perspectives of the patients (Patient Reported Outcomes or PROs) the
European Hematology Association (EHA) established a working group on QOL and symptoms
in 2006. This group is presently chaired by Professor Charles Cleeland at The University of
Texas M. D. Anderson Cancer Center and Professor Andrei Novik at the National Medical Surgical Center, in Moscow. These Chairs and their Committee will be presenting their guidelines on HR-QOL assessment and clinical application of PROs in hematology at the next EHA meeting June 4, 2009 in Berlin (Dr. T. Ionova, personal communication, March 26, 2009). In essence, these will be the first European Guidelines on PROs in hematology. No one thus far however, has addressed HR-QOL in these patients from a nursing perspective (Efficace et al, 2007).

Hematological Malignancies

Incidence and Prevalence

Hematological malignancies in adults, although relatively rare are becoming increasingly more common as the population ages. An estimated 894,543 Americans are currently living with a hematological malignancy. Of these Americans, approximately 113,000 have or have had a diagnosis of AML (31,000), ALL (56,200) or MDS (25,500) (Leukemia and Lymphoma Society, 2008; Surveillance, Epidemiology and End Results [SEER], 2007).

Acute Myelogenous Leukemia (AML) is the second most common hematological malignancy affecting adults (after Non-Hodgkin’s Lymphoma) and has an expected incidence of 13,290 patients being diagnosed in 2008 with 8,820 deaths and a five year survival rate of only 20% (National Cancer Institute (NCI), 2008). Acute Lymphoblastic Leukemia (ALL), while the most common cancer in pediatrics is more unusual in adults. The NCI estimates that 5,430 adults will be diagnosed with ALL in 2008 and 1,460 will die. ALL has an approximate five year survival of 65% but this percentage decreases dramatically with age (NCI, 2008). Similarly, of the more than 10,000 patients diagnosed with Myelodysplastic Syndromes (MDS) in 2003, 86%
were over 60 years of age and had only a 35% chance of being alive in three years (Ma et al, 2007). The exact number of people affected by MDS is unknown as there is no registry that tracks these cases (American Cancer Society [ACS], 2007).

Pathophysiology of Acute Leukemia and Myelodysplastic Syndrome

Acute leukemia results in an overproduction of clonal (genetically identical) neoplastic hematopoietic precursor (immature) cells that interfere with normal cell production and differentiation resulting in bone marrow failure (Plass et al, 2008). The pathophysiology of MDS is not completely understood. What is known is that there is a dysregulation at some stage of the differentiation process. Bone marrow failure is due to ineffective hematopoiesis caused by excessive apoptosis (programmed cell death) of hematopoietic cells and is not due to a lack of hematopoiesis (Castellino and Cripe, 2008). Regardless of the abnormality in the cells this leads to an overcrowding in the bone marrow of white blood cells (WBCs) at the expense of red blood cells (RBCs) and platelets which in turn leads to anemia (fatigue, shortness of breath), thrombocytopenia (increased bleeding risk) and leukocytosis (over production of WBCs that can lead to infection, bone pain, shortness of breath, and fatigue). Each of these side effects alone or in combination can negatively affect HR-QOL.

Disease Presentation and Diagnosis

Patients with hematologic malignancies commonly present with clinical signs and symptoms due to bone marrow failure or the effects of immature circulating leukemic cells. These common signs and symptoms include fatigue, spontaneous bleeding, weight loss, fevers and night sweats. Infections related to neutropenia due either to a low or absent absolute neutrophil count (ANC) or to a defect in the functioning of the WBCs often are present along
with evidence of hemorrhage due to thrombocytopenia (gingival bleeding, epistaxis, petechiae). There may be evidence of lymphadenopathy, hepatosplenomegaly or dermal involvement (more common in AML) (Kebriaei, De Lima & Estey, 2008).

The most commonly used classifications for AML and ALL were initially developed by the French, American and British Group (FAB). The FAB classification systems divide these diseases by cell type and degree of maturation (Kebriaei, De Lima & Estey, 2008). Appendix A and B show the FAB classification systems used for AML and ALL (ACS, 2007). MDS is also classified according to the cell lineage affected and there is a great variety in survival depending on the cell line affected. The eight sub-types of MDS and their projected life expectancy are shown in Appendix C.

Today cytogenetics (chromosomal analysis of cells obtained from a bone marrow biopsy) are increasingly used to assess disease status and prognosis. Some abnormalities improve a patient’s prognosis and some worsen it to the extent that a person’s only hope for cure lies in HPSCT (Hematopoietic Progenitor Stem Cell Transplantation formerly known as Bone Marrow Transplantation). Patients must often live with the knowledge that their prognosis for survival is poor. This knowledge and the uncertainty that it causes can negatively affect a person’s psychological HR-QOL (Seiter, 2006; Pui, Robison & Look, 2008).

*Treatment Protocols and their Requirements*

As mentioned, treatment protocols for AML and ALL patients are complex, prolonged, and intense and can result in frequent hospitalizations. Even when patients are treated as outpatients, they still require careful monitoring during multiple clinic visits over the entire course of treatment. These clinic visits can vary in frequency from daily to weekly visits.
Treatment commonly involves multiple cycles of high-dose chemotherapy followed by HPSCT depending on the disease’s risk factors and the disease’s response to treatment. One example of a complex, prolonged, and intense treatment regimen used in younger adult ALL patients is the Berlin, Frankfurt, Munster (BFM) Protocol. This protocol includes the administration of a number of different chemotherapy agents and repeated hospitalizations over approximately a one year period of time before the patient even begins maintenance therapy. A description of what this protocol involves during this first year of therapy is found in Appendix D.

Younger AML patients (less than 60 years old) generally spend 4 weeks at a time as inpatients with minimal time spent outside the hospital between chemotherapy cycles (induction through multiple consolidations) with family and friends. Hospitalization can have many negative HR-QOL effects on these patients due to their inability to work during these admissions, the psychological effects of being confined and being physically isolated, being separated from their families and particularly being separated from their young children if they have them who may be a source of infection for the patient during their prolonged neutropenic states.

Treatment for older adults (over 60 years of age) is also complicated and can affect HR-QOL as standard therapies can cause an increase in treatment-related mortality out of proportion to any increase in treatment efficacy. These older patients for whom standard therapies are not well-tolerated or efficacious, must live with more uncertainty regarding their prognosis. They may also have higher symptom burden and more frequent clinic visits and hospitalizations. All of which alone or in combination can negatively affect HR-QOL (Kebriaei, De Lima & Estey, 2008).
MDS patients are given different treatment options depending on whether their disease is classified as being at low or high risk. Low risk patients may be given supportive care alone that consists of daily to weekly monitoring of blood counts and transfusions of packed red blood cells (PRBCs) when needed (Fenaux, 2005). Patients may receive epoetin alfa or darbepoetin alfa subcutaneously to stimulate their RBC production and thus increase their hematocrit (HCT) (synthetic forms of erythropoietin [Epogen®, Procrit®, Aranesp®]) which may reduce the need for transfusions. Use of these erythropoietin growth factors may reduce the number of clinic visits thus perhaps translating into an improved HR-QOL (Jäderstein et al, 2008). Higher risk patients can chose to receive supportive care alone, epigenetic therapy (DNA non-targeted therapies) or standard chemotherapy. Lenalidomide (Revlimid®) is the first and only oral medication shown to reduce dependence on transfusions and to restore normal cytogenetics in these patients, that may translate into an improved HR-QOL in these patients (Balducci, 2006). It is important to still note that these patients can only be cured by an allogeneic (donor) HPSCT. Unfortunately most of these patients are not physically able to withstand the rigors of such treatment due to their advanced age and coexisting comorbidities (Strom, Vélez-Bravo & Estey, 2008).

Another requirement of these treatment protocols is the amount of time that is involved from the patient’s perspective to adhere to the regimens and their monitoring requirements. For example, Fortner et al (2004) found that there is no such thing as a short hospital visit. 189 patients were recruited for the study if they were 18 years or older and had received primary prophylaxis for neutropenia with a growth factor one month before enrollment. The primary purpose of this exploratory 20-site community-based study was to determine how treatment and
neutropenia affected patients’ time and activities. Patients completed a semi-structured interview; the “Patient Impact Survey” developed by the first author and designed to measure typical types of activities and their time requirements during a 21-day chemotherapy cycle. Patients completed the survey once only. The majority of patients were female and Caucasian (73% and 83.5%). All had received primary prophylaxis with a CSF (Filgrastim [Neupogen®] or Peg-Filgrastim [Neulasta®]). The patients were assumed to be receiving treatment for solid tumors but diagnosis, staging and current treatment were not described. Visits in time ranged from three hours for lab work and one injection of a growth factor to approximately 109 hours for an admission for febrile neutropenia. When one considers the magnitude of the socioeconomic time component alone, this means time away from loved ones, lost salary, fatigue from traveling, the need for transportation assistance and the cost in time and lost salary for family members as well as many patients are unable to travel to the facility independently. Sherwood et al (2008) discovered that approximately 50% of patient caregivers were employed and lost hours from work that affected their own health insurance and retirement benefits.

Neutropenia and Health-Related Quality of Life (HR-QOL)

Neutropenia is potentially the most serious effect of myelosuppression due to the high mortality from febrile neutropenia (Daniel & Crawford, 2006). Studies have shown that a patient’s HR-QOL worsens at the time of the ANC nadir (lowest circulating neutrophil count prior to chemotherapy recovery) (Padilla & Ropka, 2005). Those with more extensive grade IV neutropenia (ANC less than 500 mm³) experience more pain, greater distress and more social impairment than those patients with less severe or less severe grades of neutropenia (Fortner, Houts and Schwartzberg, 2006). Chemotherapy-induced neutropenia (CIN) is linked to HR-QOL
impairments that persist even after ANC recovery and CIN causes greater deficits depending upon the length of neutropenia and the patient’s febrile status (Ozer, 2003). Febrile neutropenia increases the incidence, duration and severity of other common side effects of chemotherapy such as nausea and vomiting, fatigue and anorexia and this exacerbation of side effects has the propensity to not only delay chemotherapy treatments but also to negatively affect a patient’s HR-QOL (Ozer, 2003; Fortner et al, 2005).

Much has been written about HR-QOL in solid tumor patients and examining the effects of short-term neutropenia in these patients (Fortner, Houts, & Schwartzberg, 2006; Padilla & Ropka, 2005; Fortner et al, 2005; Ozer, 2003). Very few studies have examined the treatment and time-related requirements associated with neutropenia as Fortner et al did (2004). Fewer studies yet have examined the HR-QOL effects of the complex, prolonged, and intense treatments, treatment-related requirements, and associated prolonged neutropenia states in patients with hematologic malignancies from their own perspectives.

Fortner et al in a series of studies (2004-2006) addressed how neutropenia affects HR-QOL in patients who primarily have solid tumors being treated with standard chemotherapy regimens during their first treatment cycle. Three of these studies are discussed in chronological sequence in the following sections.

*Health-Related Quality of Life in Neutropenic Patients*

Fortner et al (2005) studied the impact of CIN (defined by the NCI common toxicity criteria, 0-4 Likert type scale) on HR-QOL in 71 patients diagnosed with primarily solid tumors (staging not described) who were being treated with one of 5 different chemotherapy regimens. The primary purposes of this study were to evaluate the relationships between HR-QOL and the
severity of neutropenia experienced during the first chemotherapy cycle, and to analyze whether patients who experienced grade IV neutropenia during this first cycle would have a greater decrease in HR-QOL compared to those who had no neutropenia (0) or less severe grades (I – III.). Chemotherapy regimens were all administered in the outpatient setting of a regional clinic in the south and consisted of standardized protocols. HR-QOL measures included the Short Form–36, the Cancer Care Monitor, the Hospital Anxiety and Depression scale (HADS) and the Psychosocial Adjustment to Illness Scale (PAIS). All scales were completed by patients on days 0, 7, 14, 21 and 28 of their first chemotherapy cycle. Data were analyzed using Chi square tests (categorical variables), and t-tests (continuous variables). Generalized estimating equations (GEE) were used to allow for the inclusion of patients with incomplete data points. All patients included in the analyses had to have complete baseline data, but could have had missing data post-baseline at particular data points in time. Since only one patient had Grade IV neutropenia at week 3, the analyses included weeks one and two only for the 21-day cycle. The majority of patients were female and Caucasian (62%, 87% respectively); 73% were married and more than 60% were high school graduates or had some college. Most on average had been diagnosed 10 months prior to participating in the study (range 5-22 months). Comorbidities were not described. 47% of the patients experienced grade IV neutropenia. The majority of these Grade IV episodes in patients occurred either during the first or second week of treatment (20% and 35% respectively). Only 6% of patients had grade IV neutropenia lasting more than one week (6/71). Only two patients experienced febrile neutropenia but they did not have to be hospitalized for treatment. Study findings indicated that when grade IV neutropenia (duration approximately seven days) was present, there were statistically significant decreases in HR-QOL compared to
baseline in pain (SF-36, P=0.001), anxiety (HADS, P=0.03) and social contact (PAIS, P=0.04) compared to patients with no neutropenia or less severe grades, and that these effects lasted even after recovery of the patient’s ANC.

In a later trial Fortner et al (2005) examined the HR-QOL of patients who experienced grade IV neutropenia (ANC less than 500 mm³) only. This prospective, qualitative study was performed to better understand the patients’ experience of developing and coping with grade IV neutropenia during a chemotherapy cycle. Participants were adult cancer patients from the West Clinic in Memphis, TN scheduled for their first cycle of chemotherapy. Interviews were conducted with 34 patients each time they experienced grade IV neutropenia during their first cycle. A total of 100 interviews were conducted in these patients. The interviews were scheduled for days 7, 10, 14 and 21 but only began when the patient developed grade IV neutropenia. The content of these interviews was not described but the interviewers who were all advanced graduate students in clinical psychology trained in asking open-ended questions and in enabling patients to elaborate on their experiences. Patients were also instructed to keep a diary of their symptoms and to monitor their temperatures at home throughout the study but adherence rates for these activities were not reported. Patients ranged in age from 27-76 years; 71% were women and 82% were Caucasian. 79% were considered to have a good performance status. The majority had a solid tumor diagnosis (e.g., breast [28%], lung [24%], lymphoma [15%], ovarian [9%], prostate [6%] and other diagnoses (18%). 37% had metastatic disease. Chemotherapy was administered in the outpatient setting and consisted of standardized protocols. 15% of patients required hospitalization for febrile neutropenia. Interview transcripts were reviewed by two raters who independently and inductively developed descriptive categories for the patient
concerns. Discrepancies were resolved by mutual agreement. There were 80 unique problem domains that were collapsed into five major HR-QOL categories. These included: 1) physical complaints (e.g., fatigue, exhaustion, feeling drained); 2) daily routine disruption (e.g., loss of routine and difficulties with household activities); 3) negative thoughts and self evaluation (e.g., worrying about cost of care, feeling useless/helpless and letting people down); 4) negative emotions (e.g., feeling down/anxious); and 5) social relationships (e.g., decreased social contact, avoiding people/crowds). The authors concluded that neutropenia was associated with numerous negative experiences in these patients receiving their first 21-day chemotherapy cycle.

In 2006 Fortner et al addressed the association among grades of neutropenia, symptom burden and QOL and whether symptom burden became worse when patients transitioned from lower grades of neutropenia (grades 0-2) to higher grades (grades 3-4). This was a prospective study that included 84 patients from nine community oncology settings. Patients had to be ≥18 years old, with any cancer diagnosis who were going to receive their first 14- or 21-day chemotherapy cycle. Patient-reported outcomes (PROs) included the Rotterdam Symptom Check List (RSCL), the Hospital Anxiety and Depression Scale (HADS), the Cancer Care Monitor – Medical Isolation Scale (CCM-MIS) and the Short Form 36 (SF-36). Both lab work and the PROs were completed on days 0, 4, 7, 9, 11, 14, and 21. Data were analyzed using a repeated measures, mixed-model analysis. The sample included 75% women with an average age of 58 years (range 36-86), 66% were Caucasian, 68% were married and 70% had completed high school and some college. The majority had breast (52%) or lung cancer (26%), although other solid tumors and NHL were present. Most patients with breast cancer had stage I or II disease whereas the other patients had cancers at later stages (stage III or IV). All patients had a good
performance status (0-1). No comorbidities were described. 23/84 patients developed grade III or IV neutropenia and required treatment with either Filgrastim (Neupogen®) or Peg-Filgrastim (Neulasta®), only two of these patients developed febrile neutropenia and none required hospitalization. Patients who had grade 3 or 4 neutropenia had significantly greater symptom burden and worse HR-QOL than patients who had less severe grades of neutropenia. Patients who had grade 3 or 4 neutropenia had significantly greater symptom distress and worse QOL (RSCL, P=0.005 and P=0.024 respectively), significantly more depression (HADS, P=0.020), significantly more social isolation (CCM-MIS, P=0.020), and worse physical and social functioning (SF-36, P=0.020 and P=0.012 respectively). Since so few patients had febrile neutropenia, this study documented for the first time the significant negative effects on symptoms and HR-QOL that severe afebrile neutropenia has in these solid tumor patients during the first cycle of treatment. These findings also suggest that the effects of afebrile neutropenia may be particularly negative on physical and social functioning in these patients.

In summary, Fortner et al’s work has demonstrated a multitude of negative effects on HR-QOL that treatment requirements and neutropenia have on these solid tumor patients during the first chemotherapy cycle. Only the first treatment cycle was studied for these HR-QOL effects. It is unknown how these HR-QOL effects might change over the course of subsequent, repeated cycles of treatment in these solid tumor patients. In addition, the majority of Fortner et al’s studies have included standard chemotherapy regimens that for the most part are not as complex, prolonged or intense as those used to treat patients with hematologic malignancies. In addition, the incidence of Grade IV neutropenia was only 48% in these solid tumor patients and the incidence of febrile neutropenia in particular was only 4.8% with only 2.6% requiring
hospitalization. These treatment-associated and neutropenic HR-QOL effects and their incidence can only be projected to be much more common and severe in patients with hematologic malignancies due the nature of their malignancies and the intended bone marrow suppression intended to eradicate the disease in the bone marrow. A major goal of therapy for patients with AML, ALL and MDS is prolonged grade IV neutropenia. Fortner et al make the repeated case for conducting further research using larger sample sizes, patients who may experience more severe grades of neutropenia and to evaluate specific relationships among physical symptoms, neutropenia, and their psychosocial effects from these patients’ perspectives (PROs).

Health-Related Quality of Life in Patients with Leukemia or Myelodysplastic Syndromes.

It is challenging to assess HR-QOL in the patient newly diagnosed with acute leukemia or MDS due to the aggressive treatment regimens that often result in the very same symptoms as the disease itself causes. Treatment involves chemotherapy that is directed at the bone marrow and killing all malignant cells. This process reduces the number and the maturation levels of all cells in the bone marrow. This process leads to prolonged neutropenia, anemia and thrombocytopenia and the very symptoms the patient had prior to their diagnosis. As a consequence, patients often experience long periods of time in which they are unable to observe any clinical benefits from the treatment. In general, the HR-QOL of patients during the induction phase of their treatment is worse than in those patients who are in remission and are undergoing consolidation and maintenance treatments. These HR-QOL differences may be due to a reduced disease burden and perhaps patients having a better understanding of what’s involved in the treatment process. The first few months following the diagnosis are especially problematic for these patients as they are often required to stay in the hospital for prolonged periods of time and
financial hardships may occur due to lost wages and the cost of the expensive treatments (Redaelli et al, 2003).

HR-QOL is an important area to assess and study particularly prior to treatment in the elderly patient with hematologic malignancies due to their high risk of mortality with standard therapies (Oliva, Latagliata et al, 2008; O'Connor et al, 2007; Redaelli et al, 2003). Oliva, Latagliata et al (2008) presented data at the American Society of Hematology (ASH) meeting (December, 2008, San Francisco) addressing HR-QOL in 113 elderly (over 60) AML patients over a period of 12 months. In this study, HR-QOL at diagnosis was found to be a prognostic factor for overall survival and thus was recommended to be assessed prior to making a treatment decision.

Efficace et al (2007) went so far to suggest that there is a general school of thought that compromising a person’s HR-QOL was an indispensible step towards achieving a cure in these patients and that the treatment’s effect on HR-QOL was an indication of its success! This theory is believed to have evolved from the need to treat these patients quickly and aggressively as often there are only hours that elapse between the diagnosis of the patient’s disease and when the patient begins initial intense chemotherapy. This is in sharp contrast to the care offered to patients with solid tumors. Hematologists have perhaps believed that they have limited to no time available to delay the start of treatment that obtaining a formal baseline PRO HR-QOL assessment might require. This might be another factor that perhaps has hindered HR-QOL assessments and PRO research in these patients.
Measurement of Health-Related Quality of Life

There are many scales that can be used to measure HR-QOL. The choice of which instrument to use depends on scientific and practical considerations such as the sample size, literacy, costs, difficulties associated with administering and scoring instruments and availability of resources to help with data collection and analysis (Padilla, Frank-Stromborg & Koresawa, 2004).

To date there are more than 800 generic or specific tools that purport to measure HR-QOL (Cella et al, 2002). For example, the Functional Assessment of Chronic Illness Therapy (FACT) contains multidimensional HR-QOL items to measure HR-QOL in patients experiencing chronic illnesses including cancer. There are now multiple disease- and symptom specific FACT modules available for solid tumors such as lung, breast, and colorectal cancer, and for leukemia and neutropenia. The FACT-Neutropenia questionnaire has been validated by Wagner et al (2007) and Lathia et al (2008). Fortner et al (2006) also have validated a tool specifically for measuring symptoms and treatment-related side effects, the Cancer Care Monitor (CCM. This measure has shown a high sensitivity and specificity in trials when the same questions are asked of patients and specialized oncology nurses. These tools will be further evaluated in the SIP.

Summary

In summary, this ROL documents the dearth of studies related to HR-QOL in hematologic patients and the international interest in beginning to advance the science in this understudied area (Efficace et al, 2007). Studies addressing HR-QOL in neutropenic and hematology patients have to date, treated HR-QOL from the assumption that HR-QOL will automatically improve once the WBC recovers. There are no studies evaluating HR-QOL effects
in patients who will be functionally neutropenic for a prolonged period of time, who may never recover their counts, and who may suffer from a reduced HR-QOL the remainder of their lives. There are also no studies that evaluate care given by an APRN to improve the HR-QOL of adult patients with AML, ALL or MDS.

Many studies call for the urgent need to further evaluate HR-QOL (Alibhai et al, 2007; Steensma et al, 2007; Fortner et al, 2004; Sherwood et al, 2008) in these patients. However, there needs to be more evidence-based guidelines and procedures that can be tested for their HR-QOL effects. To date such studies have not been undertaken particularly from the perspectives of the roles an APRN might play in this area. Thus the decision to conduct this ROL to provide the foundation for my future SIP.
CHAPTER 3 - DISCUSSION

The review of literature described in Chapter 2 has shown that there is a distinct lack of research into the HR-QOL of adult patients with AML, ALL and MDS. Nurses at both the bedside and at the advanced practice level are well positioned to care for these patients and to improve the patient’s HR-QOL during and after treatment. This chapter reviews the roles that an APRN can play in mitigating the negative HR-QOL effects of these treatment requirements and associated prolonged neutropenic episodes in these patients.

Clinical Implications for Nursing

Although there are few studies conducted in this area, there is evidence that bedside nurses caring for hematology patients have articulated interest in learning more about caring for these kinds of patients who are experiencing prolonged treatment regimens and associated neutropenia. Nurses also are expressing frustration at the lack of formal education available in this understudied area (King, 2008). In King’s (2008) study, nurses viewed HR-QOL and neutropenia as high priorities for nursing research, they believed that many nurses do not have the knowledge or skill to care for these patients and are therefore not able to intervene in a manner that can positively affect HR-QOL outcomes in these patients. The creation of a formal educational program for bedside nurses is well within the scope of practice for an APRN and could be included as part of a research protocol evaluating HR-QOL in these patients.

Fortner et al appreciated the roles that nurses potentially could play in this area. These authors indicate that one of the roles could be in minimizing the disruption that treatment may cause for patients and their families by serving as a liaison (triaging of which symptoms need to
be reported and which patients require more frequent monitoring) between patients and physicians. These authors further suggest that protocols and guidelines need to be developed to guide nurses to assess, intervene, and promote HR-QOL in patients with neutropenia especially those patients with prolonged and more severe grades of neutropenia (grades 3-4).

Advanced Practice Registered Nurse Roles in Promoting Health-Related Quality of Life

Many studies have documented that the care delivered by NPs is equivalent and sometimes superior to that offered by physicians. Although not all of these studies specifically address the care of patients with cancer they do report that patients are better educated, have greater perceived autonomy, report symptoms earlier, have quicker and safer post-operative discharges (APRN homecare intervention was effective in enhancing survival), fewer readmissions post discharge (Cunningham, 2004) and receive improved continuity of care (Howell et al, 2008).

In lung cancer patients McCorkle et al (1989) documented considerable improvement in symptom distress, functional status and current concerns in patients receiving care from an APRN. This suggests that an APRN has the potential to prevent and/or mitigate certain symptoms and complications by providing effective symptom assessment and management strategies. Unfortunately there are few studies that have investigated APRN roles in caring for patients with cancer and none that have considered the roles that an APRN might play in mitigating the negative HR-QOL effects that occur in the care of adult patients with AML, ALL or MDS.

The majority of studies and articles that describe the roles a nurse can play in HR-QOL do not address the role of the APRN. In two articles Ropka and Padilla (2005 and 2007) suggest
that the currently available HR-QOL and neutropenia tools may not be suitable for clinical practice. These authors recommend that an individualized-focused, neutropenia-specific QOL questionnaire be developed to guide interventions in this area. The APRN could evaluate the strength and quality of the evidence in planning care and by using this information to design and implement evidence-based programs.

Nurse Coordinator and Patient Navigator roles assure a patient’s access to care and improve communication and continuity of care (Jackson, 2008; Schwaderer & Itano, 2006; Wells et al, 2008). These are roles that are appropriate for an APRN to implement after receiving additional education in the care of the cancer patient.

*Nursing and Neutropenia*

Controversy exists over the care of neutropenic patients and the prevention of infections. There are evidence-based guidelines for the use of colony stimulating factors (CSFs) in patients with CIN (American Society of Clinical Oncology, 2006) and for caring for patients with febrile neutropenia (Infectious Disease Society of America, 2002). However, there are no definitive guidelines for the management of outpatients with neutropenia who are not receiving CSFs and are not febrile. Recommendations have been made for having 24 hr access to an oncology registered nurse, meticulous follow-up to prevent infections (Crighton, 2004) and family involvement (education, vigilance and balancing responsibilities with ongoing family life) (Eggenberger et al, 2004). Nirenberg et al (2006) states that there are considerable gaps in the evidence in the areas of practice, research and education related to the prevention and management of neutropenia, a point substantiated by Cunningham (2004), King (2008) and Atkinson and Tawse (2006). The NCCN (2008 and 2009) and Oncology Nursing Society (2006)
have published guidelines for the care of cancer patients with infections, neutropenia and the use of growth factors. These guidelines will be reviewed in more depth in the SIP.

**Project Limitations**

This literature review was limited by including only articles in English. As a consequence, there may have been articles available in other languages related to these areas of interest that were not evaluated.

**Recommendations for Future Study**

Because of the lack of HR-QOL studies particularly from the viewpoint of the patients (e.g., PROs), future studies need to collect PRO data that evaluate patient-identified needs and perceptions of what they believe has been lacking in their current care. Based on this baseline data, a protocol could be designed, implemented and evaluated by an APRN and others to determine its affects on HR-QOL in these patients.

**Conclusions**

While several studies in this ROL Master’s Degree Project have addressed HR-QOL, none have addressed HR-QOL or the role of an APRN in its promotion in adults with hematologic malignancies receiving treatment for prolonged periods of time and prolonged neutropenic episodes. Many of these studies have called for further study in this area, but as Levine and Ganz (2002) said, while we’ve become very good at measuring a patient’s HR-QOL we are not very good at implementing or evaluating a program or protocol to improve HR-QOL in these patients. Such an interdisciplinary program or study led by an APRN could be an outcome of the planned Scholarly Inquiry Project.
## Appendix A

*French American British (FAB) Classification of AML*

<table>
<thead>
<tr>
<th>FAB subtype</th>
<th>Name</th>
<th>Approximate % of adult AML patients</th>
<th>Prognosis compared to average for AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Undifferentiated acute myeloblastic leukemia</td>
<td>5%</td>
<td>Worse</td>
</tr>
<tr>
<td>M1</td>
<td>Acute myeloblastic leukemia with minimal maturation</td>
<td>15%</td>
<td>Average</td>
</tr>
<tr>
<td>M2</td>
<td>Acute myeloblastic leukemia with maturation</td>
<td>25%</td>
<td>Better</td>
</tr>
<tr>
<td>M3</td>
<td>Acute promyelocytic leukemia</td>
<td>10%</td>
<td>Best</td>
</tr>
<tr>
<td>M4</td>
<td>Acute myelomonocytic leukemia</td>
<td>20%</td>
<td>Average</td>
</tr>
<tr>
<td>M4 eos</td>
<td>Acute myelomonocytic leukemia with eosinophilia</td>
<td>5%</td>
<td>Better</td>
</tr>
<tr>
<td>M5</td>
<td>Monocytic leukemia</td>
<td>10%</td>
<td>Average</td>
</tr>
<tr>
<td>M6</td>
<td>Acute erythroid leukemia</td>
<td>5%</td>
<td>Worse</td>
</tr>
<tr>
<td>M7</td>
<td>Acute megakaryoblastic leukemia</td>
<td>5%</td>
<td>Worse</td>
</tr>
</tbody>
</table>

Adapted from American Cancer Society (ACS, 2007) with permission
APPENDIX B

French American British (FAB) Classification of ALL

<table>
<thead>
<tr>
<th>FAB Subtype</th>
<th>Approximate % of Adult ALL Patients</th>
<th>Immunologic Type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>30%</td>
<td>T cell or pre-B cell</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>65%</td>
<td>T cell or pre-B cell</td>
<td></td>
</tr>
<tr>
<td>L3</td>
<td>5%</td>
<td>B cell</td>
<td>Poor prognosis with standard therapy. Also called Burkitt's Lymphoma</td>
</tr>
</tbody>
</table>

Adapted from American Cancer Society (ACS, 2007) with permission
APPENDIX C

*MDS Types and Survival Rates in Years*

<table>
<thead>
<tr>
<th>Type</th>
<th>Median Survival in Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia</td>
<td>5.5</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts</td>
<td>5.5</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>3</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts</td>
<td>3</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
<td>1.5</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>3.7</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>10</td>
</tr>
</tbody>
</table>

Adapted from American Cancer Society (ACS) (2006) with permission
**APPENDIX D – Berlin Frankfurt Munster (BFM) Protocol**

Reprinted from USC Norris Cancer Hospital. (2001). BFM Protocol from Trial 9L-03-1

<table>
<thead>
<tr>
<th>MODIFIED BFM WORKSHEET</th>
<th>NAME:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDUCTION PHASE I</strong></td>
<td>Day 1 = _________ (date)</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>60 mg/m² IV</td>
</tr>
<tr>
<td>Vinccristine (max 2)</td>
<td>14 mg/m² IV</td>
</tr>
<tr>
<td>PEG-Asparaginase</td>
<td>2000 U/m² IV</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² PO</td>
</tr>
<tr>
<td>MTX (IT)</td>
<td>12 mg IT</td>
</tr>
<tr>
<td><strong>INDUCTION PHASE II</strong></td>
<td>Day 28 = _________ (date)</td>
</tr>
<tr>
<td>Cytospan</td>
<td>1 g/m² IV</td>
</tr>
<tr>
<td>ARA-C</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td>Vinccristine (max 2)</td>
<td>1.4 mg/m² IV</td>
</tr>
<tr>
<td>PEG-Asparaginase</td>
<td>2000 U/m² IV</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>60 mg/m² PO</td>
</tr>
<tr>
<td>MTX (IT)</td>
<td>12 mg IT</td>
</tr>
<tr>
<td>Prednisone</td>
<td>20 mg/m² PO</td>
</tr>
<tr>
<td><strong>CONSOLIDATION I</strong></td>
<td>Day 1 = _________ (date)</td>
</tr>
<tr>
<td>HD-MTX</td>
<td>1 g/m² IV except T-ALL 2.5 g/m² IV</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>15 mg q 6th IV</td>
</tr>
<tr>
<td>At least 8 doses</td>
<td>2000U/m² IV</td>
</tr>
<tr>
<td>PEG-Asparaginase</td>
<td>20 mg/m² PO</td>
</tr>
<tr>
<td>Prednisone</td>
<td>12 mg IT</td>
</tr>
<tr>
<td><strong>CONSOLIDATION II</strong></td>
<td>Day 1 = _________ (date)</td>
</tr>
<tr>
<td>ARA-C</td>
<td>75 mg/m² IV</td>
</tr>
<tr>
<td>VM-26</td>
<td>60 mg/m²</td>
</tr>
<tr>
<td><strong>DELAYED RE-INDUCTION I</strong></td>
<td>Day 1 = _________ (date)</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>25 mg/m² IV</td>
</tr>
<tr>
<td>Vinccristine</td>
<td>1.4 mg/m² IV</td>
</tr>
<tr>
<td>Desmethylasenase</td>
<td>10 mg/m² PO</td>
</tr>
<tr>
<td>PEG-Asparaginase</td>
<td>2000 U/m² IV</td>
</tr>
<tr>
<td>Cytospan</td>
<td>1 g/m² IV</td>
</tr>
<tr>
<td>ARA-C</td>
<td>75 mg/m² IV</td>
</tr>
<tr>
<td>6-Thioguanine</td>
<td>60 mg/m² PO</td>
</tr>
<tr>
<td>MTX (IT)</td>
<td>12 mg IT</td>
</tr>
<tr>
<td><strong>CONSOLIDATION III</strong></td>
<td>Day 1 = _________ (date)</td>
</tr>
<tr>
<td>HD-MTX</td>
<td>1 g/m² IV except T-ALL 2.5 g/m² IV</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>15 mg q 6th IV</td>
</tr>
<tr>
<td>At least 8 doses</td>
<td>2000U/m² IV</td>
</tr>
<tr>
<td>PEG-Asparaginase</td>
<td>20 mg/m² PO</td>
</tr>
<tr>
<td>Prednisone</td>
<td>12 mg IT</td>
</tr>
<tr>
<td><strong>CONSOLIDATION IV</strong></td>
<td>Day 1 = _________ (date)</td>
</tr>
<tr>
<td>ARA-C</td>
<td>75 mg/m² IV</td>
</tr>
<tr>
<td>VM-26</td>
<td>60 mg/m²</td>
</tr>
<tr>
<td><strong>DELAYED RE-INDUCTION II</strong></td>
<td>Day 1 = _________ (date)</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>25 mg/m² IV</td>
</tr>
<tr>
<td>Vinccristine</td>
<td>1.4 mg/m² IV</td>
</tr>
<tr>
<td>Desmethylasenase</td>
<td>10 mg/m² PO</td>
</tr>
<tr>
<td>PEG-Asparaginase</td>
<td>2000 U/m² IV</td>
</tr>
<tr>
<td>Cytospan</td>
<td>1 g/m² IV</td>
</tr>
<tr>
<td>ARA-C</td>
<td>75 mg/m² IV</td>
</tr>
<tr>
<td>6-Thioguanine</td>
<td>60 mg/m² PO</td>
</tr>
<tr>
<td>MTX (IT)</td>
<td>12 mg IT</td>
</tr>
<tr>
<td><strong>MAINTENANCE (SEE PROTOCOL)</strong></td>
<td>Day 1 = _________ (date)</td>
</tr>
</tbody>
</table>
REFERENCES


