CHAPTER 2

LITURATURE REVIEW

2.1 Impact of Non-communicable Disease Worldwide and Policy Implementation

According to the World Health Organization (WHO) Report 2002, the non-communicable diseases were estimated to contribute nearly 60% (37.7 million) of the death cases throughout the world, where 43% are the global burden of disease. The report also expected the increasing trend for the year 2020 to account for 73% of deaths and 60% of disease burden. In other words, every three out of four deaths worldwide will be related to non-communicable diseases (WHO, quoted in Murray and Lopez, 1996) in which the low and middle-income countries would suffer the greater impact. In 1998, the developing countries had experienced the 77% of total deaths from non-communicable disease and 85% of disease burden befall in low and middle-income countries (WHO, 1999). Over 9 million people worldwide had found cancer in 1997 and more than 6 million died from it. Death from cancer had increased from 6% of total deaths from 1985 to 9% in 1997 in developing countries (WHO, quoted in Men, Ageing and Health, 1999).

Thailand, as a middle-income country, has found a death from cancer as a second cause of death in non-communicable disease (WHO, cited by Popkin, Horton and Kin, 2001). Cancer rates in Thailand had doubled up from 1.5% in 1960s to 3.2% in 1970s and to 9.3% in 1990s. Several forms of cancer can be prevented and effectively treated with early detection. For example, healthy lifestyles and elimination of potential risk factors such as smoking may implicate pesticides causing incidence of leukemia and lymphoma. The rising incidences of non-communicable disease in almost all economic classes in countries worldwide merit and extensive evaluation for the cost of treatment in order to justify important policies to enact

Report of the Leukemia, Lymphoma, and Myeloma progress (Review group, 2001), also taken together of Leukemia, Lymphoma, and Myeloma (LLM) constitute the fourth most common form cancer. Despite advances in diagnosis and treatment and improvements in patient survival, the Hematological cancers continue to have a significant impact on the lives of Americans. Currently, almost 700,000 Americans are living with Leukemia, Lymphoma, or Myeloma (LLM), and estimating 100,000 new cases to increase every year. Although mortality has declined and 5-year survival rates have increased among adults and children with certain forms of these diseases, an estimated 60,000 Americans died of them in 2001.

Among all forms of Leukemia, the five-year survival rate is containing 46%, Non-Hodgkins Lymphoma is 54.2%, and Multiple Myeloma is only 28%. Despite the significant decline in the death rate for children with leukemia, this disease still causes more deaths in children in the U.S. than any other disease. Furthermore, the death rates for Non-Hodgkin's Lymphoma and Multiple Myeloma are increasing at a time when death rates for other cancers are dropping. Since the 1970's, incidence rates for Non-Hodgkin's Lymphoma have increased dramatically, making it one of the fastest rising cancers in the United States. The Hematological cancers strike individuals of all ages, from children to the elderly, men and women, and all races. The decreases in mortality that have occurred in recent decades reflect the progress that has been made in understanding and combating LLM. Disease pathogenesis and pathophysiology of the hematological malignancies are better understood than in most other cancer subtypes. Standard radiation and chemotherapy can cure disease in a substantial fraction of patients with Acute Myeloid Leukemia (AML), Acute Lymphocytic Leukemia (ALL), Anaplastic large-cell and other Lymphomas, and Hodgkin's lymphoma.

Furthermore, it will soon be possible to achieve a molecular classification of Myeloid and Lymphoid malignancies that also incorporates a pathologic and clinical understanding of disease. New technologies, including genome-wide surveys of gene

expression patterns and genetic alterations, have already resulted in changes to the classification of hematological neoplasm and will result in the recognition of new disease entities and potential prognostic markers. In addition, a large number of potential targets for intervention are already available, and the development of treatments for the hematological malignancies can serve as a prototype for the development of therapy for solid tumors.

The National Cancer Institute (NCI) has furthered this advancement through its programs and initiatives that facilitate drug discovery, development, and testing, including clinical evaluation of products and exploration of novel agents. Findings from NCI-supported basic research have identified a plethora of potential therapeutic targets for further exploitation. Perhaps the most striking example in any cancer of the benefit of molecularly targeted therapy is all-trans retinoic acid for Acute Promyelocytic Leukemia. As the application of chemotherapy in the hematological malignancies led the way to improved chemotherapy for all cancers, so the development of these molecularly targeted therapies will serve as an important model for curing all cancers. Thus, a major expansion in translational research in the hematological malignancies will provide a benefit for relieving the burden of cancer that far exceeds the frequency of these diseases.

At the Greenlandic Nuna Med 2000 Conference on public health in Nuuk, Greenland, September 2000, Burden of Disease and Cost-Effectiveness in health planning by Lasse Christian Nielsen, 2000 claimed that the decision maker need the best available evidence to address the burden of disease in population. In order to archive a future scenario of maximum health gain from available resources, an intimate strategic approach to identify the control priorities is recommend.

1) Quantify the burden of disease and injury as well as its causes in terms of risk factors and broader health determinants using the best available method;

2) Identify health inequalities by examining differences in the burden of disease by age, sex, area of residence and socio-economic status;

3) Calculate likely disease burden in the future;

4) Assess the available evidence for various types of health interventions;

5) Combine knowledge regarding the extent of current and future health problems with knowledge regarding ability of health services and multi-sectoral interventions to respond to these health challenges;

6) Apply Cost-Effectiveness Analysis of current and potential new health interventions in order to determine the most efficient combination of relevant health interventions (health package) in relation to the available resources.

The approach of combined usage is a powerful tool to assist the decision making at all levels in society. This recommends the application of the approach to define the control priorities and essential packages of care in the light of experience gained by practical application in the health care sector in Greenland. WHO-launched burden of disease methodological approach aims to;

1) Dissociate epidemiological assessment of the magnitude of health problem from advocacy by interest groups of particular health policies or interventions;

2) Include in health policy debates information on non-fatal health outcomes along with information on mortality;

3) Undertake the quantification of health problems in time-based units that can also be used in economic appraisal, thereby supporting objective (1).

These three goals articulated for the Global Burden of Disease 1990 also remain central to the Global Burden of Disease 2000 project (Nielsen, cited by Global Burden of Disease, 2000).

2.2 The influence of Health Insurance Coverage of Bone Marrow Transplant

The adverse impact of low socio-economic status on the access to care (Selby et al., 2001) treatment, and outcomes of nonmalignant and malignant diseases has been well recognized. Attempting to illuminate such an effect by completing a retrospective analysis of all patients with AML-CR1 (n = 30) or AML-CP1 (n = 29) that received 6 antigen-matched sibling donor marrow transplants at the University of Oklahoma from June 1986 through June 1998. Minimum follow-up was 16 months (ranging 16-167 months). They used the type of insurance coverage as a surrogate for socio-economic status and denoted patients with commercial or Medicare coverage as insured/non-poor and patients with Medicaid or no insurance as under-insured/poor.

Patient characteristics and outcomes are displayed in Table 2.1. Differences were seen only at more than 100 days to 16 months. They believe this phenomenon of delayed mortality likely represents the under-insured/poor patients' inability to comply with or seek medical care because of deficient socio-economic resources. During the early post-transplantation period, when the under-insured/poor patients are in hospital, the resources of a comprehensive Health Sciences center can compensate for their socio-economic deficiency, but an increased risk of death occurs after they return to their pre-transplantation social setting.

Table 2.1: Patient Characteristic and Outcome

	Insured/ Non-poor (n = 45)	Under-insured/ Poor (n=14)	P
Age, μ (mean ±SD)	36.8 ±11.8	27.0 ±16.3	0.017*
Non-Caucasian	18% (8/45)	43% (6/14)	0.075#
Diagnosis AML	49% (22/45)	57% (8/14)	0.590°
Bone Marrow Transplant (year)			0.467#
1986-1990	16 (36%)	3 (21%)	
1991-1995	17 (38%)	8 (57%)	
>1995	12 (27%)	3 (21%)	
Acute GVHD grade III-IV	16% (7/45)	0% (0/14)	0.181#
Extensive chronic GVHD	39% (16/41)	30% (3/10)	0.462#
Mortality <30 day	2% (1/45)	7% (1/14)	0.421#
Mortality 30-99 days	7% (3/44)	23% (3/13)	0.125#
Mortality 100 days to < 16 months	15% (6/41)	50% (5/10)	0.027#

*Independent t test.

#The Fisher exact test.

°Chi-square test.

There could be profound implications for the public funding of stem cell transplantation. In addition, socio-economic status would join other established prognostic factors describing "high-risk" patients that are relevant to the reporting of institution-specific outcome results.

Many patients continue to be denied from Autologous and Allogeneic stem cell transplants (Tones et al., 2000). Although medically and clinically accepted for certain disease states, blood and marrow transplantation continues to be viewed as investigational or experimental by some third-party payer. Managed care organizations in particular are frequently reluctant or unwilling to reimburse medical procedures that they

perceive to be novel, investigational, or more expensive than Conventional therapies. Coverage of Bone Marrow Transplant patients varies throughout the United States (Ballen et al., 1998), This study show that not only the money that require for the Bone Marrow Transplant, but the highly skill of health personals are included also. Personal involved in supportive care of Bone Marrow Transplant patients include fellows, medical house-staff, nurse practitioners, physician assistants and moonlighting physicians. According to the surveys collected from 108 American and Canadian transplant centers on the composition of inpatient support team, the mean number of transplants performed annually at each center was 101 (range 4-515). Where the day-time coverage 57% of fellows, 50% of medical house-staff, 35% of nurse practitioners, 25% of physician assistants, and 0% of moonlighting physicians, while the night-time coverage of 50% of fellows, 56% of medical house-staff, 7% of nurse practitioners, 6% of physician assistants, and 13% of moonlighting physicians. Involvement by medical house-staffs included 44% of 24-hour coverage, 8% of night-time coverage, 18% of stat coverage, and 21% of code blue coverage. Medical house-staff was similar in small and large transplant programs, involved more in university-based programs.

Health care providers are concerned increasingly with the effectiveness and efficiency of their health care systems. One approach to this problem is to make increasing use of technology assessment, evaluating costs and outcomes of alternative interventions (Barr, 2002). A review of published reports, to be presented in detail, yields the following summation. The greater cost of stem cell harvest from peripheral blood is more than offset by the reduced costs associated with a shorter hospital stays. Transplants early in first remission cost less than those undertaken at later points in disease evaluation/treatment experience. Changing the primary locus of care from inpatient to outpatient may result in notable cost saving, but can produce cost-shifting (from inpatient to outpatient). Nevertheless, in selected patient, the use of Non-Myeloablative transplants may offer a cost-effective option, especially in the developing countries.

2.3 The Cost-Effectiveness Analysis

The current health care expenditures in United States are rising and contributing about 15% of GDP, about 8-9% of GDP in the Netherlands and about 6-7% of GDP in United Kingdom (Williams and Stolk, quoted in OECD Health data, 1997). Total health expenditures are increasing extensively. As a matter of facts, It is not possible to fund every possible treatment while the decision makers expect to maximizing the result in term of best medical outcomes per unit. The clinical evaluation studies are different from economic evaluation (Williams and Stolk, 2003). The clinical evaluation and economic evaluation show different perspectives. The clinical evaluations intend to optimize resource use within a specified patient group and concentrate on finding which alternative treatment improves health most. The economic evaluations intend to optimize resource use across a whole spectrum of patient groups, to evaluate outcomes across the spectrum of conditions and treatment. This is why the economists have to apply a common standard such as a cost-effectiveness, not the clinical effectiveness, into play to measure whether it worth the cost.

Cost-Effectiveness Analysis is a common tool used for decision support on which medical care should be offered (Barnett, 2002). It is a method of comparing the cost and effectiveness between two or more alternatives. Such comparisons are useful when one of the alternatives being considered is standard care, as this allows the decision maker to consider whether an innovation is better than status quo. Cost-Effectiveness studies of two interventions will be essential when the choices between an innovation and standard care must be made. The analyst first applies the principle of strong dominance that either the innovation or standard care may be preferred using this principal. Strong dominance favors a strategy that is both more effective and less costly. Strong dominance occurs only when the innovation is worth (in terms of performance and disbursement). While the effective innovation and cost is similarly arising, but the strong dominance provides no guidance. The decision makers must decide if the greater effectiveness is worth for

achieving it. And this could be done by a calculation of an incremental cost-effectiveness ratio. The criteria for assessing cost-effectiveness are deviated upon different healthcare systems and countries.

2.4 Hematological Disorder Selected following by Bone Marrow Transplant Criteria under Social Security Scheme, Thailand

1) Severe Aplastic Anemia

Incidence: 5-10 case per million persons per year (Harrison's Principles of Internal Medicine 14th international edition volume1, part six Oncology and Hematology, Hugo Castro-Malaspina, Richard J. O'Reilly) 1,000 new cases per year in USA.

Prognosis:

- Transfusion support alone will provide the mortality rate up to 80% and die in 18 to 24 months.

- Immunosuppressive Therapy patients have included 60% to 80% partial remission, 1/3 relapse, and 20% to 50% develop Myelodysplastic Syndrome.

- Bone Marrow Transplant has been curative in 60% to 90% of patients with long term survival. Chronic Graft Versus Host is a major and lethal complications, it depends on age and degree of matching.

Treatment:

- Immunosuppressive Therapy: ATG provided 20% to 30% achieve complete blood count, response rate is about 50% to 70%, and partial response is about 70% to 80%.

- Bone Marrow Transplant: HLA-matching sibling is about 25% to 30% with current survival rate 70% to 90%, in early study there is graft failure 20% to 30%.

- Bone Marrow Transplant: HLA-matched with unrelated donor by National Marrow Donor Program and the European donor banks over 2 millions volunteers give the

donated marrow up to 20% of total patients, there are high incidence of Acute Graft Versus Host and Chronic Graft Versus Host, and survival rate is about 30%.

Current Medical Diagnosis & Treatment 1997, 36th Edition, Appleton & Lange

- Medial Survival with out treatment is average at 3 months and 20% of patients are survival for 1 year.
- Treatment of choice is Allogeneic Bone Marrow Transplant, it gives the best result in young adults.
- Treatment of choice for adult > 50 years old without HLA-Identical is Immunosuppressive Therapy.
- Allogeneic Bone Marrow Transplant gives the 80% Complete Remission in children and young adults.
- Allogeneic Bone Marrow Transplant gives the 50% to 80% of Complete Remission in older adult or previous expose blood product patients.
- Chemotherapy gives the partial response about 60% and long-term prognosis good, while there is about 25% turn to Myelodysplasia Syndrome.

2) Acute Non-lymphocytic Leukemia (ANLL) in First Complete Remission or Acute Myeloid Leukemia (AML).

Incidence: Approximately 2.3 cases per 100,000 per year (male=2.9, female=1.9), increasing incidence with increasing age (incidence = 1.3 with age < 65, incidence = 12.2 with age > 65).

Prognosis:

- Bone Marrow Transplant: under age 65 without major organ dysfunction who have HLA-matched and age < 55 years old will be cured about 40% to 60%.

- Chemotherapy: there is no significant difference over all survival rate, but tends to lower risk of relapse in Bone Marrow Transplant than Chemotherapy.

- Some patients with HLA-matched not undergo Bone Marrow Transplant.

- Higher incidence of treatment-related complication after Bone Marrow Transplant.

- Availability of better salvage therapy for intensive Chemotherapy patients with relapse (i.e., Bone Marrow Transplant)

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- Found in adult age > 50 years old that the more increasing age and the more increasing incidence of disease.

- 70% of adult and age < 60 years old will have the 70% to 80% of Complete Remission.

- 70% of adult and age > 60 years old will have about 50% of Complete Remission.

- Chemotherapy curative rate is 30% to 40%.

- Allogeneic Bone Marrow Transplant provide the 60% curative rate, while the Autologous Bone Marrow Transplant gives the curative rate roughly 50% to 70%

3) Chronic Myeloid Leukemia (CML) in Chronic Phase

Incidence: Approximately 1.3 cases per 100,000 per year (male=1.7, female=1.0), increase in incidence when age going to middle forties rapidly.

Prognosis: 10% of patients died within 2 years and median survival ~ 4 years.

Sokal Index indicates the Prognostic Indicators and composed of the followings

- Percentage of circulating blasts when >3% of blood and >5% of bone marrow.

- Spleen size is about 10 cm.

- Pletelets count is more than 700,000.

- Cytogenetic clonal evolution, the basophile is more than 7% of blood and more than 3% of bone marrow.
- The age over 60 years old.

Treatment

- Allogeneic Bone Marrow Transplant: this is only curative therapy reported by International Bone Marrow Transplant Registry, benefits in survival for Allogeneic Bone Marrow Transplant seen after 6 years.
- Depend on Patient factors: Age, Phase of disease, Type of donor, Syngeneic;twins, HLA-compatible, Related or unrelated donor, Preparative regimen, Graft Versus Host Disease, Post-transplantation Treatment.
- Syngeneic of Bone Marrow Transplant will be provided about 55% of 7-years-disease-free with 30% of relapse rate.
- HLA-indentical sibling in chronic phase of Bone Marrow Transplant will be provided about 40% to 70% of 5-years-disease-free with 25% of relapse rate.
- HLA-matched unrelated donor by Seattle group of Bone Marrow Transplant will be provided 74% probability of surviving at 3 years, but less than 1 year after diagnosis with age under 50 years with 2-years-disease-free.
- Survival rate about 45% ± 21% for unrelated with matched or mismatched 1 locus of Bone Marrow Transplant by National Marrow Donor Program.
- Unrelated donor of Bone Marrow Transplant provided that increase in graft failure, increase of Acute Graft Versus Host, Chronic Graft Versus Host and convalescence.
- Related donor of Bone Marrow Transplant prefers to give the better result than unrelated donor due to Allogeneic hematopoietic progenitor cells.
- Chemotherapy will be provided about 30% to 50% complete cytogenetic response but short lived. If they are almost undergo Autologous Bone Marrow Transplant following that will be at 31% complete remission and median lived about 14

months (2-68 months). This intervention gives a better result than Conventional therapy.

Current Medical Diagnosis & Treatment 1997, 36th Edition, Edited by Lawrence M. Tierney, Jr., Stephen J. Mcphee, and Maxine A. Papadakin (Appleton and Lange)

- HLA-Identical sibling (matched related donor) will be provided about 60% long-term-disease-free-survival in adults and the best result must be done after diagnosis for 1 year about 70% to 80% of long-term-disease-free-survival.

- HLA-Identical without sibling donor will be provide about 40% to 60% of long-term-disease-free-survival.

- Median survival of patient is about 3 to 4 years.

4) Acute Lymphocytic Leukemia (ALL)

Most common found in children, young adult

Incidence: 1 per 100,000 per year, male > female, and white > black.

Treatment

- Chemotherapy provided about 50% to 85% of Complete Remission and 40% of 5-years-survival.

- Bone Marrow Transplant and Chemotherapy give as much as the same result in first remission unclear with 45% of 5-years-survival with 3-years-disease-free.

- If the disease was relapsed, the prognosis with Bone Marrow Transplant could be very poor, and the survival rate is only 20% to 30%.

Adult with ALL will have poorer result in Chemotherapy than children, but the first remission shows not much improvement. Bone Marrow Transplant provided the better treatment and outcome than Chemotherapy.

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- Peak Incidence in Children 3-7 yr. old (80% of total Leukemia in children and 20% of total Leukemia in adult)
- 80% of adult have completed remission in Chemotherapy
- 30-50% curative rate in chemotherapy
- BMT with Allogeneic, age <50 after relapse = 30-40%
- BMT with Autologous, after 2nd remission = 30-50%

5) Non-Hodgekin's Lymphoma (NHL)

Incidence: 45,000 new cases per year in USA and number of patients are increased about the fourth cancer title of person-year-of life lost and increase in exponential from AIDS related Lymphoma.

Treatment

- The early stage treatment with radiotherapy will be provided about 60% to 80% of 5-year-survival and uncommon to use Chemotherapy.
- 23% of patients were not spontaneous remission, should done following with Chemotherapy.
- Chemotherapy will be provided about 30% to 60% of Complete Remission and median remission for 2 years.
- Patients with intermediate, or high-grade NHL relapse or fail complete remission are poor prognosis, the Complete Remission rate is about 20% to 30%, 30% of partial remission and remission period about 2 to 6 months.
- Bone Marrow Transplant provided about 40% of long-term-disease-free-survival.
- 30% to 50% of patients with relapse, or end-stage after treatment were 40% to 50% of 5-year-disease-free-survival.

Current Medical Diagnosis & Treatment, 36th Edition, Appleton and Lange

- Medial Survival of pts = 6-8 years
- Curative 50% with appropriate therapy
- 50% cure with Autologous BMT
- resistant with Chemotherapy in aggressive Lymphoma

6) Multiple Myeloma (MM)

Incidence: 4 per 100,000 people around the world (male > female, and incidence of black is double to white)

Prognosis

- 15% of patients died in 3 months after diagnosis, death rate is about 15% of total patients per year.
- In acute terminal phase, the prognosis is worse. The survival time is less than 6 months.
- 46% of total death is in the chronic phase.

Treatment

- Chemotherapy will be provided about 50% of Complete Remission with standard treatment (complete response rate < 10%).
- Allogeneic Bone Marrow Transplant will give the higher response rate than Chemotherapy but treat-related mortality about 40%.

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- Medial Survival of mean average of every condition is about 3 years.
- Medial Survival with good prognostic factor is 3 to 6 years.
- Medial Survival with bad prognostic factor is only one year.
- Allogeneic Bone Marrow only produces the curative treatment.

2.5 Review of Previous Results in Different Condition of Bone Marrow Transplant

1. T-cell-depleted Unrelated Donor Bone Marrow Transplantation for Acute Myeloid Leukemia (Mark et al., 2000).

The outcome for 39 patients with Acute Myeloid Leukemia (AML) in remission who would compatible with 1M T cell-depleted unrelated donor Bone Marrow Transplant, that are engrafted primarily. Severe viral infection was the major complication and occurred 12 episodes in 9 patients, 5 of them lethal. 25 patients survive at a median follow-up of 44 months (2-102 months), with estimated actuarial overall rates at 44 months of 61% (SE 8%) and disease-free survival rates at 57% (SE 8%). 19 patients are more than 2 years post-Bone Marrow Transplant and may be cure, with excellent long-term survivors. 19 of 21 patients can survive for 6 months or longer in full-time employment or full-time students. These encouraging results suggest that in patients lacking a sibling donor, unrelated donor Bone Marrow Transplant for AML in remission achieves survival figures as good as those reported on patients with Autologous stem cell transplant, and that T-cell depletion of graft is associated with a low relapse rate.

2. Early Outcome after Allogeneic Stem Cell Transplantation for Leukemia and Myelodyplasia without Protective isolation: A 10-year experience (Russell et al., 1999)

Although it is a common practice to use some forms of isolation to protect Allogeneic stem cell transplant patients from infection, the necessity for the practice in all environments has not been demonstrated. This study evaluated patterns of infection and 100-day transplant-related mortality in 288 patients with Myelodysplasia and Leukemia transplantation without isolation. 10% of patients had a clinical infection where most of infections were endogenous; blood cultures from 24% of recipients grew organisms, 87% is gram-positive bacteria. 1% of patient died with aspergillus that isolable would not have

been helpful. 20% of patients had no evidence of infection. Transplant-related mortality at 100-day was 1% for 108 patients in low risk group and 21% in higher risk group. It is to conclude that the Allogeneic stem cell transplantation can be safely performed in some environments without confining patients continuously to the hospital.

3. Morbidity and Mortality of Chronic Graft-versus-Host Disease (CGVHD) after Hematopoietic Stem Cell Transplantation from HLA-identical Sibling for Patients with Aplastic or Refractory Anemia. (Goerner et al, 2001)

This study analyzed effects of successive changes in prevention and treatment of CGVHD in 405 patients with Aplastic Anemia and refractory anemia given HLA-matched hematopoietic stem cell transplantation (HSCT) from 1970-1997. Patients were divided into groups: group I(1984-1990), group II(1977-1983), group III(1984-1990), and group IV(1991-1997). Incidence of CGVHD for group I through IV were 20%, 46%, 41% and 22%, respectively reflecting added buffy coat infusion in group II and III. The overall incidence of CGVHD was 28%. In conclusion, over 28 years, CGVHD has remained challenging, with only slightly improvements in quality of life. Decisive improvement of therapy should be understood the immunological events underlying CGVHD and better infection prevention and control.

4. Marrow Transplantation from Unrelated Donors for Patients with Severe Aplstic Anemia (SAA) who failed immunosuppressive therapy. (Deeg, 1999)

Allogeneic Marrow Transplantation offers curative therapy for patients with Aplastic Anemia. Retrospective results in 141 patients with SAA who received transplants between 1998-1995 from unrelated volunteer donor identified through the nation marrow donor program (NMDP). 105 patients (74%) received HLA-matched marrow and 36 patients (26%) received marrow mismatched for at least one HLA-A, -B, or -DR antigen. Currently, 51 patients (36%) after transplantation patients with donor matched by both serology and

allele-level DRB1 typing had significantly shown greater survival than 56 DRB1-mismatched patients 15% surviving at 3 years. The outcome of patients with greater delay in transplant is even worse. Major causes of death were graft failure, GVHD, and infection. The data suggests the unrelated marrow transplant will offer successful therapy for a proportion of patients who have failed immunosuppressive therapy.

5. A Retrospective Comparison of Allogeneic Peripheral Blood Stem Cell and Bone Marrow Transplantation Results from a Single Center: A focus on the incidence of Graft Versus Host Disease (GVHD) and relapse. (Ustiin et al, 1998)

Detecting the effect of the stem cell source, Allogeneic Peripheral Blood Stem Cell Transplantation (allo PBSCTs) performed between 1995 and 1997 from HLA-identical sibling in 40 patients with acute and chronic hematological disorders were used to compare a historical group of 40 patients with similar variable that received Allogeneic Bone Marrow Transplant (allo BMT) between 1993 and 1995. The estimated disease-free survival in month 24 was 51.3% for allo BMT and 54.6% for allo PBSCT, and estimated overall survival in month 24 was 56.1% for allo BMT and 64.6% for allo PBSCT. In conclusion, the retrospective comparison suggests that allo PBSCT from HLA-identical donors are associated with faster engraftment, few transfusions but no greater incidence of Acute GVDH, and high incidence of Chronic GVHD.

6. Successful Unrelated Marrow Transplantation for Patients over the Age 40 with Chronic Myelogenous Leukemia (CML). (Drobyski et al., 1998)

Some older patients ($\geq$ 40 years) with CML and without HLA-identical sibling are not offered unrelated marrow transplantation due to over excessive regimen-related toxicity concerning GVHD. This study determines the efficiency and toxicity of unrelated marrow transplants in older CML patients using a regimen designed to minimize the severity of GVHD. 31 consecutive patients over the age of 40 with CML received unrelated

marrow transplant between January 1988 and June 1997. 21 patents were transplanted in chronic phase while 10 were transplanted in accelerated phase. Older CML patients who have HLA-identical or one antigen mismatched unrelated donor can successfully undergo Allogeneic marrow transplant. T cell depletion of marrow graft may be advantageous in these older patients by reducing GVHD severity, particular in those patients transplanted with HLA-disparate marrow grafts.

7. Update report: Non-Myeloablative Bone Marrow and Peripheral Blood Stem Cell Transplant. (Muthu, 2002)

There is no reliable evidence to compare overall safety and effectiveness of Non-Myeloablative treatment with other management strategies of patients considering eligible or ineligible for Myeloablative transplant. The current update does not show substantive incident in the conclusion of the original report. However, identification of three poorly controlled studies. These provide weak evidence to compare with Myeloablative treatment, where Non-Myeloablative transplant may reduce infection related mortality in all recipients and transfusion requirements in short term survivors. Conclusions are unreliable because of likely biases, including confounding by baseline difference between treatment groups. In the absence of well controlled studies, with defined inclusion criteria, pre-stated outcomes and standardized intervention protocols, Non-Myeloablative transplant remains an experimental treatment.

8. Cyclophosphamide and Antithymocyte Globulin in condition patients with Aplastic Anemia for Allogeneic Marrow Transplantations: The experience in four centers. (Storb et al, 2000)

This report summarizes the experience with a conditioning regimen of Cyclophosphamide and Antithymocyte Globulin in patients with Severe Aplastic Anemis given HLA-matched marrow grafts at 4 transplantation centers. 94 patients, of whom 87

received multiple transfusion and 38 patients failed immunosuppressive therapy. Age rise from 2 to 59 years, a median follow-up is 6.0 years (range 0.5-11.6 years) and the survival rate was 88%. Conclude that the Cyclophosphamide/Antithymocyte Globulin regimen combined with methotrexate/cyclosporine after transplantation is well tolerated effective inheavily pretreated patients with Aplastic Anemia.

9. Bone Marrow Transplantation (The merch manual et al. diagnosis and therapy, 2004).

Patients with AML or ALL may be benefits from Bone Marrow Transplant, AML are in first remission about 50% to 60% likelihood of long-term disease-free survival similar to ALL in the first remission. Probability of relapse correlates with remission status at the time of transplantation, ranging from 20% to 60% with more advanced disease. Long-term survival for patients with CML who receive Bone Marrow Transplant in the phase of remission is about 60% to 70%.

10. For Bone Marrow Transplant Survivors, it is much better than previous thought. (Heberman and Bush, 2004)

The survey of 125 patients undergo marrow transplants before June 30, 1983, was one of the largest quality of life studies of marrow transplant survivors of any kind and it is the only study to assess 6 to 18 year survivors available. More than 90% of the respondents claim leading full, meaningful lives and average of 10 years after transplant. 88% report that the benefits of transplant outweighed side effects. Most of them were back to work or school. 77% of patients were ranked their current physical health in excellent condition. 5% reported a low quality of life similar to the general population. Pessimistic perception of medical professionals is that most of the literature reviewing on marrow transplant survivors focuses on the late medical complication procedures. Handful of

previous studies focusing on the global quality of life, and none of those looked in any detail at survivors beyond 4 years post-transplant.

11. Chemotherapy Compared with Autologous or Allogeneic Bone Marrow Transplantation in the Management of Acute Myeloid Leukemia (AML) in first remission. (Cassileth et al., 1998)

The study started in February 1990 and ended in February 1995, the data were analyzed as of August 1997. Eligible 740 from 808 patients were 16 to 55 years old and had untreated AML of French-American-British (FAB) types M0 to M7. There is no significant difference in disease-free survival among patients receiving high-dose chemotherapy, those undergoing Autologous Bone Marrow Transplant and those undergoing Allogeneic Bone Marrow Transplant. The median follow-up was 4 years. Survival after complete remission showed better result after chemotherapy than Autologous marrow transplantation. There was a marginal advantage in term of overall survival with chemotherapy when compared will Allogeneic marrow transplantation. This is to conclude that a post induction course of high does Cytarabine can provide equivalent disease-free survival and better overall survival than Autologous marrow transplantation in adults with AML.

12. Short-term and Long-term Effects of Acute Myeloid Leukemia on Patient Health-Related Quality of Life. (Redaelli A, et al., 2004)

The survey identified 21 articles, AML associated treatments have a substantial negative impact on patient health related quality of life (HRQL) as has been measured by several different leukemia specific, cancer specific and generic instruments. The most negative HRQL burden appeared shortly after the diagnosis of the disease and during the course of therapy (aggressive therapies e.g. chemotherapy or bone marrow transplant etc.) Long-term survivors appeared to recover HRQL almost completely with respect to

physical, psychological and emotional well being, but incur continued sexual dysfunction. In conclusion, clinical responsible for the care of patients with AML should be aware of the HRQL impact of the disease and its treatment, the long-term and the short-term.

2.6 The Previous Study of Cost-Effectiveness Analysis of Bone Marrow Transplant in Other Countries.

The cost-effectiveness of Bone Marrow Transplant therapy and its policy implications by S.O. Schweltzer, Ph D. and C. C. Scalzi, R. N., M. N./Scholl of public health university of California, shows a relative new medical technology used in the treatment of Aplastic Anemia and Acute Leukemia. Similarly, a kidney transplant can replace a diseased kidney and the transplanted bone marrow can replace a diseased bone marrow. The bone marrow is the site of production of red blood cells, white blood cells, and platelets. In the severe form of Aplastic Anemia the bone marrow ceases to function.

The data used to compare the effectiveness of BMT and Conventional Therapy employed sources from UCLA Bone Marrow Transplant in Severe Aplastic Anemia and in Acute Leukemia, Lancet, October 1978 and December 1977 for Actual survival of Aplastic Anemia and Acute Leukemia given conventional therapy. The cost also obtained from the UCLA Health Science Record System for every third BMT patient treated at UCLA between 1974 and 1978. Cost-Effectiveness ratios for Bone Marrow Transplant for lives saved in Aplastic Anemia was $105,755 per life and in Acute Leukemia was & 277,239 per life. For extended years of life in Aplastic Anemia was $1,995 per year and in Acute Leukemia was $5,231 per year.

Analysis of the data with these limitations shows that the means of short-term quality of life for 24 patients with Aplastic Anemia is 1.6 and is slightly lower at 1.3 for 23 patients with Acute Leukemia. Less than half the patients in either group survived 1 year

post-transplant, so the sample for long-term quality of life is very small. The means of long-term quality of life for 9 patients with Aplastic anemia is 2.7 and for 10 patients with Acute Leukemia is 1.9.

The Cost-Effectiveness Analysis of Bone Marrow Transplantation compared with conventional chemotherapy in Japan, (Nakahara N1 et al) shows the assessment of the Cost-Effectiveness on Leukemia, Malignant Lymphoma, Multiple Myeloma, and children solid tumors in Japan. The direct medical costs in 3 years for BMT undertaken in domestic clinical trials with 40 patients (26 adults and 14 children) where additional data for costs, including probabilities, were employed from published literature in Japan.

A decision analytic model with decision trees was used to estimate the average direct medical cost in three years. Regarding therapeutic effectiveness, Japan used the Declining Exponential Approximation of Life Expectancy (DEALE) method to estimate the expected life years of survival. The cost estimation included the direct medical cost and the mortality cost. Sensitivity analyses were performed to test the results. As a result, the average costs in 3 months associated with the domestic clinical trials were estimated to be 6,072,866 Yen for adults and 5,276,643 Yen for children with respect to Bone Marrow Transplant.

Consequently, the total costs in 3 years with the decision analytic model were estimated as 26,760,804 Yen per patient for BMT and 23,296,564 Yen per patient for chemotherapy. The life expectancy was 6.28 years per patient for BMT and 4.25 years per patient for chemotherapy. The cost-effectiveness ratios (cost per life year gained) were 4,261,274 Yen for BMT and 5,355,532 Yen for chemotherapy. Since the incremental cost was 3,464,240 Yen when comparing BMT with chemotherapy, the incremental cost-effectiveness ratio was eventually estimated to be 1,794,943 Yen. The cost-effectiveness analysis was conducted based on the cost data in Japan, and concluded that BMT was more cost-effective than conventional chemotherapy.