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APPENDIX I

Social Security Office in Thailand

Insurance for catastrophic and non catastrophic health care are one of the benefits under social security scheme through the risk pooling of all members. Moreover, employers as well as the government have also financed in the scheme. The beneficiaries can obtain the health care coverage whenever they get sick without anxiety over how much it would cost.

In Thailand, the social security scheme has been introduced to ensure financial security and reduce inequity in accessibility to health care of the formal sector employees. Contribution of 1.5 percent of insurable earning are made by employers, employees and the government, these contributions fund for 4 types of benefits namely;

- 1.1 Sickness Benefits
- 1.2 Maternity Benefits
- 1.3 Invalidity Benefits
- 1.4 Death Benefits

These four benefits were implemented in the initial stage of scheme. In response to prevailing economic concerns, the rate was temporarily reduced from 1.5 percent to 1 percent for period 1998 to 2003

Pension and child allowance benefits had been implemented effective on 31 December 1998. Additional contributions of 1 percent each for employees, employers and the government were made for the old-age pension and child allowance scheme. The contribution rate was increased to 2 percent and will increase to 3 percent each for employees and employers for period 2000 to 2002 and 2003, respectively the share of the government will continue to remain at 1 percent

Unemployment benefits will start in 2004, the contribution rate is 0.5 percent each for employees and employers. Respectively, the share of government is 0.25 percent.

Contributions are based on actual earning up to a maximum of 15,000 baht per month. Minimum contributions are based as the level of minimum wage. Employee who paid contribution not less than 3 months within 15 months prior to the date of receiving care are entitled to receive sickness benefits which are comprise of medical care including cash benefit.

Social insurance coverage under the Social Security Act

In Thailand, Social Security Act was enacted on 1 September 1990 and implementation started 6 months later. In March 1991 the government, employees and employers started to make contributions to the Social Security Fund. The fund is administered by a tripartite Social security board consisting of 15 members, constituted by each five representatives from employers, employees and the government. The social security office (SSO) under the ministry of labor acts as the secretariat of the board. This compulsory scheme initially covered the employees of establishment with 20 employees or more. Now, the scheme is extend to one employee already.

However, the scheme is not applicable to;

1. Public officials, permanent employees, daily temporary employees and hourly temporary employees of central administration, provincial administration and local administration but excluding monthly temporary employees.
2. Employees of foreign government or international organizations.
3. Employees of employers who have offices in the country and being stationed aboard.
4. Teachers or headmasters of private schools under the law on private school.
5. Students, nurse students, undergraduates or intern physicians who are employees of schools, universities or hospitals.
6. Other activities or employees as may be prescribed in the Royal Decree.

Health care benefit package

In determination of health care benefit package of the social security scheme, there is a medical committee consisting of qualified persons in the field of medical science.

The committee has duties to give advices on medical matter as well as to determine criteria and health care benefit package to the SSO. However, the social security committee has over all responsibility for the scheme. Therefore, the health policy advice by the medical committee has to be approved by the social security committee.

Although Thailand has not ratified the ILO Convention No. 102 on the social security yet, health care benefit package was determined to cover the essential medical services. This health care provision for insured persons cover;

- Primary health care and immunization.
- Secondary health care both for inpatients and outpatients.
- Tertiary health care in case of the specialist care and high medical technology as the following;
 1. Diagnostic and treatment services until the end of treatment.
 2. Hospitalization, including treatment, accommodation and food.
 3. Drug and pharmaceuticals as determined at least by the national drug list.
 4. Referral system from health case provider to specialist services.
 5. Health promotion and prevention through health education and immunization according to the national immunization program.

However, there are the exclusions of care provided in case of the following conditions;

1. Psychiatric disease, except during acute illness with in 15 days period of care.
2. Disease of injury from drug abuse.
3. Long-term illness which requires inpatients care exceeding 180 days per year.

4. Hemodialysis, except for acute renal failure which requires immediate treatment for not more than 60 days and end stage of chronic renal failure.
5. Aesthetic treatment which no medical indication.
6. Treatment which is being on experimental study.
7. Treatment for infertility.
8. Tissue examination for organ transplantation, except for Bone Marrow Transplant.
9. Unnecessary examination.
10. Transplant surgery.
11. Sex interchange or transsexual surgery.
12. Artificial insemination in case of infertility.
13. Service during rehabilitation process.
14. Dental care, except pulling, filling, and scaling.
15. Spectacles and contact lens

Health care provider network

The hospitals that are qualified with the criteria must sign a contract with the SSO. They will be the 'main contractors". SSO will pay the medical service fee to the hospital as the method and rate determined, This will be mentioned in the next chapter.

Besides the provision of care of the main contractor, the facility of the accessibility of insured persons is also taken into the consideration. The capitation system might restrict the insured persons in their choice of hospital and it might take them a long time to receive a common-illness or primary care treatment. The SSO, therefore, authorizes the main contractor to improve its accessibility by subcontracting services. A crucial reason to create subcontractor is that SSO aims to provide a nearby access for the insured persons. In response to the standard of the main contractor and also economic circumstance of the country, it is more costly to provide ambulatory care by the main hospital than by small health care provider.

It is therefore suggested to have an agreement with "Subcontractors". The main contractor will subcontract any health care provider who needs to provide services. Small hospitals, private clinics or polyclinics can be subcontractors if they are qualified. The person entitled to medical care services can have a better access. The promotion of subcontracting can improve the primary medical care services for insured person. The main task of a subcontractor is to look after patients at the primary stage. If the subcontractor is unable to do so, the patient has to be transferred back to their main contractor. The main contractor will be responsible to pay for the medical service fee for those as mentioned in the agreement.

For tertiary care, some main contractors may not be able to provide all of the services, such as a complicated disease case. There is a supporting referral system created. It is a system which refers patient to another health provider that can provide more specialized services. These services are referred to "Supra contractor". The expenditure during the reference will be the responsibility of the main contractors. The distinction of the care level is shown below.

Provider	Level of care			Payer to provider
	Primary	Secondary	Tertiary	
Subcontractor	✓			Main contractor
Main contractor	✓	✓		SSO
Supra contractor			✓	Main contractor

Provider payment in social insurance scheme in Thailand

From international experience, it was found that there were the success and failure in health care operation and economic circumstance. Furthermore, operation in health care is the most difficult aspect in social insurance administration. The payment method

should be appropriate to the economic circumstance of the country as well. The SSO has adopted the capitation payment as the main component for provider payment system with contracted hospital-based providers. It was because a result of financial constraints during the scheme's inception and of administrative simplicity and expected health care cost. Furthermore, it would not affect to health care expenditure of the country in the long term period.

Under the capitation payment, SSO will pay the amount of capitation to the contracted hospital based on the number of registered insured persons regardless of the sickness prevailing. The contracted hospital could be in either public or private ownership, the choice of contractor hospital was initially given to the employer. Afterward, the employee choice had been phased in gradually. Until 1997, all employees can select their own hospital membership all over the country.

When insured person selects the hospital, the SSO will issue a medical card that should be used to identify the entitlement for the medical services. SSO has set the guideline that insured persons must register themselves in contract hospitals for the period of two years. After one year, the insured persons can change the contracted hospitals if they need.

The original capitation fee applied in mid -1991 was 700 Baht / person / year based on the costs of the relevant health care components and the target utilization in 1991/1992. The rate was derived from the assumptions of 3 ambulatory visits and 0.5 hospitalization days per capita per year, and unit costs of 150 Baht per outpatient visit and 500 Baht per hospital days as the following.

$$\begin{aligned}\text{Capitation fee} &= (150 * 3) + (500 * 0.5) \\ &= 700 \text{ Baht / person / years}\end{aligned}$$

The original capitation fee had not been adjusted for five years since its implementation because the utilization rate of insured person did not reach the level which the capitation fee was made and it appeared that the hospital can profit from the arrangement.

In 1995, there was the proposal of the capitation fee adjustment. The fee was adjusted by the average inflation rate of 1991-1995 (10-11%). Then, the capitation fee was raised from 700 Baht to 800 Baht in January 1996 and that fee was implemented until 1997.

In 1997, Thailand has been affected by the economic crisis. The capitation fee was also reviewed in order to be in accordance with devaluation of Baht and health care cost of the country. In January 1998, the flat rate capitation fee was adjusted to be differential capitation fee according to the number of insured persons registered. The fee applied for contract hospital were 1,000 Baht if there was 1-50,000 insured persons and 900 baht in case 50,001 insured persons up. In mid 2000, the capitation fee was adjusted to become flat rate again in the amount of 1,100 Baht per year.

Practically in the capitation system, capitation fees are pre-paid monthly. A monthly capitation amount is estimated on the basis of the number of registered insured persons at the beginning of each month; then, 75 percent of estimated capitation amount is paid in that month. In the next month, the actual monthly capitation amount is calculated based on the actual average number of insured persons of the previous month, and the difference between the actual amount and the 75 percent of the estimated amount of the relevant month is paid.

The simple formula for capitation payment can be expressed as follows:

$$\text{Preliminary amount} = N_1 * \frac{C}{12} * \frac{75}{100} \dots\dots\dots[1]$$

$$\text{Actual amount} = \left[\frac{N_1 + N_2}{2} \right] * \frac{C}{12} \dots\dots\dots[2]$$

Thus, the difference = [2] - [1]

where:

C = Capitation fee

N_1 = Number of insured persons at the beginning

N_2 = Number of insured persons at the end of the month

Although the aims of operation of capitation payment system are cost containment and stability of the fund, the quality of care is also taken into the focusing. The creation of the assurance for quality of care is necessary under such system. Apart from the hospital accreditation for screening the hospital before entering into the scheme, it is the responsibility of the SSO to make sure that contracted hospitals still maintain their standard and quality of care provided under capitation. The SSO has the group of medical professions to monitor and evaluate the medical care provided by contracted hospital periodically during the year. This proactive quality assurance arrangement is a significant measure for monitoring and controlling the appropriateness of care regarding the medical principle.

According to the concept of capitation payment, this method is a significant measure for SSO to control health care expenditure. Nevertheless, the capitation system performs some disadvantages. The hospitals' revenue from capitation is fixed based on the number of insured persons registered with the hospital. The more services the hospital provides, the higher the expenditure of the contracted hospital it is. The hospital might tend to minimize their services in order to avoid the risk of loss. One way of controlling under-servicing for the SSO is to introduce other sub-systems of payments in order to reduce the risk of the contracted hospital and to facilitate the accessibility of insured persons as well.

The other sub-systems of payment that have been implemented apart from capitation payments are as the following.

1. Payment for special high cost services

To provide care to the beneficiaries, there might be some cases which require special treatments. However, it is costly for the hospital as well. If it occurs, the hospital will face the risk of loss. So, it is possible that contracted hospitals provide under-servicing to SSO's beneficiaries. This is a disadvantage of the capitation payment. Thus, in order to avoid the risk of loss to the hospital, SSO should be partially responsible for high expenditure. This additional payment is apart from capitation fee which SSO paid to the contracted hospital. The payment will be paid as the reimbursement rate which determined by the Medical Committee. However if the expenditure exceeds the determined rate, it has to be the responsibility of the hospital.

The list of the special treatments and the reimbursement rate are shown below.

Item	Reimbursement Rate
1. Actual Renal Failure (not exceeding 60 days)	
- Hemodialysis	3,000 Baht/time
- Peritoneal Dialysis	1,500 Baht/day
2. Chemotherapy or Radiotherapy for Malignant patients	30,000 Baht/year
3. Open Heart Surgery	100,000 Baht/case
4. Implantation of Prosthesis and Instrumentation	As items and rate of SSO announcement
5. Brain surgery	
- Craniotomy or Craniectomy	15,000 Baht/case
- Craniotomy or Craniectomy with Complication	30,000 Baht/case

- Craniotomy or Craniectomy due to Unconscious Patient	30,000 Baht/case
- Craniotomy or Craniectomy with Special Instrument	30,000 Baht/case
6. Coronary Bypass	100,000 Baht/case
7. Percutaneous Balloon Valvuloplasty	20,000 Baht/case
8. Cryptococcal Meningitis Treatment - Medicine only	15,000 Baht/case
9. Coronary Dilatation using Balloon or Percutaneous - Transluminal Coronary Angioplasty	30,000 Baht/case (not exceed 2 times)
10. Vasectomy (for Male) Tubal Ligation (for Female)	500 Baht/case 1,000 Baht/case

Note: US\$ 1 = 42.49 Baht (June 2002)

2. Payment for accident and emergency care

Accident and emergency cases might take place in remote area which is far from the contract hospital. In this case, the insured person can not receive care from the selected hospital immediately. Therefore, the insured person can be admitted by any of the hospitals. The cost of the necessary medical care within 72 hours (excluding the official holiday) in non-contracted providers is reimbursed by the SSO. For emergency case, the number of reimbursements either outpatient or inpatient care is restricted to not exceed 2 times per person per year. Otherwise, it risks that members will go for emergency treatments of simple or common illness. In case of accident, the number of reimbursements in public hospital is not restricted whereas the number and rate of reimbursement in private hospital are determined the same as in emergency case.

The items and rate of reimbursement for accident and emergency care are as the following.

Item Reimbursement Rate

Emergency Case

(Within 72 hrs.)

1. Outpatient (not exceed twice a year)
 - Treatment 300 Baht / visit
 - Laboratory Examination 200 Baht / visit
 - Physician Procedure 200 Baht / visit

2. Inpatient (not exceed 2 admissions / year)
 - Treatment 1,500 Baht / day
 - Major Operation (< 2 hrs.) 8,000 Baht / time
 - Major Operation (> 2 hrs.) 15,000 Baht /time
 - Room and Board 700 Baht / day
 - ICU Treatment 2,000 Baht I day
 - CT scan and or MRI 4,000 Baht I visit

Accident (within 72 hrs.)

1. Public Hospital
 - Treatment Full amount as necessary
 - Room and Board 700 Baht I day

2. Private Hospital same as emergency case

In the case of accident and emergency in non-contracted hospital, the contracted hospital must be informed urgently in order that it will not be the burden for insured person in payment or in case the expenditure exceeds the reimbursement rate.

When the registered hospital is informed, it has the following duties.

- (1) In case the patient can be movable, the registered hospital has the responsibility to cover such cost of medical care in non-registered hospital since the time it has been informed.
- (2) In case the patient can not be movable;
 - If the contracted hospital is informed within 72 hours, the contracted hospital has the responsibility to cover the cost of medical in non-registered hospital only for amount exceeding the reimbursement rate since the time it has been informed up to 72 hours.
 - If the contracted hospital is informed after 72 hours, the contracted hospital has the responsibility to cover the cost of medical since the time which has been informed.

3. Payment for utilization incentive

In 1996, an additional payment was added as an incentive payment in order to compensate hospital with relatively high utilization when compared with all hospital. This extra - capitation payments are based on outpatient and inpatient caseloads. A utilization relating payment is paid to the contracted hospitals which submit monthly clinical information on utilization and medical service costs. SSO uses the percentile ranking system to compare the utilization of all contracted hospitals. The annual amount of payment ranges from 30 Baht/ person to 100 Baht/person. The hospital that submitted the information not less than 7 months a year can receive this payment. Higher percentiles result in higher additional payment. The rate of payment can be expressed as follows:

$$\text{Pr } 0 - \text{Pr } 30 = 30 \text{ Baht/person/year}$$

Pr 31 -Pr 40 = 40 Baht/person/year

Pr 41 -Pr 50 = 50 Baht/person/year

Pr 51 -Pr 60 = 60 Baht/person/year

Pr 61 -Pr 70 = 70 Baht/person/year

Pr 71 -Pr 80 = 80 Baht/person/year

Pr 81 -Pr 90 = 90 Baht/person/year

Pr 91 -Pr 100 = 100 Baht/person/year

Utilization rate per year of each hospital is calculated as follows:

$$\sum_{i=1}^{12} \left(\frac{N_{1i} + (N_{2i} * N_{3i} * 4.97)}{N_i} \right)$$

where:

N_i = Average of persons registered in month

N_{1i} = Number of visits of OP

N_{2i} = Number of admissions of IP N_{3i} = Average length of stay i = Month 1 , 2 , 3 ...12

Note: 4.97 is constant value. According to the research, inpatient expenditure is 4.97 times larger than that of outpatient.

4. Payment for diseases or items which were determined specifically

In order to look after the insured person for the exemption in the benefit package, the SSO determines some diseases or items that can be reimbursed specifically as the following.

- Dental care can be reimbursed in case of pulling, filling and scaling in any provider. The reimbursement rate is not exceed 200 Baht/time and not exceed 400 Baht/year.
- Bone marrow transplantation (according to the determined criteria) in the particular specialist institution will be capitated in the amount of 750,000 Baht/case and tissue biopsy of such case can be reimbursed not exceed 7,000 Baht/case.

- Hemodialysis in case of end stage of chronic renal failure can be reimbursed not exceed 1,500 Baht/time and not exceed 3,000 Baht/week.
- Artificial lens can be reimbursed 4,000 Baht/side.

5. Payment for risk adjusted

In recognition that the capitation payment system shifts the financial risk to the contract hospital, in 2001 the SSO also added case-mix risk adjusted payment. Hospitals are received this payment according to the risk rate of all inpatient admission and the determined chronic disease of outpatient. The overall amount of payment is equal to 150 Baht times the average number of insured persons of all hospitals.

Diagnostic Related Grouping (DRG) is used to adjust for the case-mix of inpatient while the score is given to the following chronic diseases of outpatient.

1. Diabetes Mellitus
2. Hypertension
3. Chronic Hepatitis and Cirrhosis
4. Congestive Heart Failure
5. Cerebrovascular Accident
6. Malignancy
7. AIDS & HIV
8. Chronic Obstructive Pulmonary

The combination of capitation payment and sub - systems, therefore, can encourage the contracted hospitals to develop their quality of care continually. For this reason, it interests their member for choosing them in the next further years. If the hospitals can maintain their members or level of their market share, this can reduce the risk of loss of the hospitals. Eventually, there is the strengthening and the quality of the capitation system.

APPENDIX II

Bone Marrow Transplant

Bone Marrow Transplant, Harrison's Principles of Internal Medicine Hematopoietic stem cell transplantation is usually carried out for one of two reasons:

1. To replace an abnormal but not malignant marrow that has been purposefully destroyed with either radiation or chemo therapy, or
2. To allow for the administration of higher than usual doses of myelotoxic chemotherapy and/or radiation therapy to treat a malignancy.

The types of bone marrow abnormalities treated with this procedure include both congenital and acquired diseases; the malignancies treated with hematopoietic support include acute leukemias and lymphomas, as well as solid tumors that appear to have a dose-response curve to chemotherapy. The source of hematopoietic stem cells may be the bone marrow, peripheral blood, cord blood, or fetal liver of another individual, generally one who is immunologically matched at the major histocompatibility complex .

Table 8: Disease treated with Hematopoietic Stem Cell Transplant

Malignancies	Allogeneic	Autologus
Acute leukemia (lymphoblastic or myelogenous)	+	+
Chronic myelogenous leukemia	+	+
Myelodysplastic syndrome	+	-
Lymphoma	+	+
Multiple myeloma	+	+
Chronic lymphocytic leukemia	+	+
Breast cancer	-	+

Allogeneic and Syngeneic Bone Marrow Transplant

Allogeneic bone marrow transplantation is usually restricted to person less than 60 years of age. The results tend to be poorer in older patients because of increased complications associated with graft-versus-host disease (GVHD) in this population. However, the patient's general health is also very important, and many transplantation groups make decisions about intervening on the basis of the patient's physiologic rather than chronologic age.

For patients without a twin, an HLA-matched sibling donor is the best choice for an allogeneic bone marrow transplantation. The genes for the HLA antigens are found on chromosome 6. One would expect that the HLA type would follow the rules of mendelian genetics, namely, that any two siblings would have one chance in four for sharing the same HLA type. Except for an approximate 1 percent chain crossover (a switch in genetic material between chromosomes during meiosis), this is in fact the case, forming the basis for HLA family typing. Because of the relatively small size of American families, only about 30 percent of Americans have an HLA-identical sibling. The formula for calculating the chance that a particular person has an HLA-matched sibling is $1 - (0.75)^n$, where n denotes the number of potential sibling donors.

For patients who may benefit from an allogeneic bone marrow transplant but lack an HLA-matched sibling donor, there are two possible solutions. One is to identify an unrelated but closely HLA-matched person willing to donate marrow or peripheral blood, and the other is to use marrow from a related donor who is less than perfectly matched. The extremely large number of possible HLA phenotypes (the number of theoretical possibilities is larger than the total world population) makes the search for an unrelated donor a difficult undertaking. Fortunately, in patients with a similar genetic background,

certain HLA phenotypes occur more frequently than might be expected based upon random population genetics.

Preparation for Transplant

High doses of chemotherapy with or without radiation therapy are delivered to the recipient with two main goals: destruction of the residual malignant or dysfunctional cells and destruction of the immune system of sufficient degree to avoid rejection of the allograft by residual, immunologically active cells in the host.

Table 9: Prevention of acute Graft-versus-Host disease

<ul style="list-style-type: none"> •Histocompatibility matching of donor and recipient •Sterile environment
<ul style="list-style-type: none"> •In vivo prophylaxis
<p>Cyclosporine ± methotrexate ± prednisone</p> <p>Antithymocyte globulin</p> <p>FK-506</p>
<ul style="list-style-type: none"> •In vitro marrow T cell depletion
<p>Antibodies ± complement</p> <p>Immunotoxins</p> <p>E-rosette depletion</p> <p>Lectin treatment</p> <p>Immunoabsorbent column separation</p> <p>Elutriation</p>

The Transplantation Procedure

Collection of bone marrow from a donor is referred to as harvesting. Marrow is usually harvested by repeated aspiration from the posterior iliac crest until an adequate number of cells has been removed. If a sufficient number of cells cannot be obtained from the posterior iliac crest, marrow can also be harvested from the anterior iliac crest and sternum. If peripheral blood stem cells are being harvested, the donor may receive a colony stimulating factor (CSF) to augment the number of circulating stem cells and then will undergo repetitive apheresis procedures lasting several hours on consecutive days. The risk to the donor is very slight and predominantly associated with the risk of the anesthesia used. The procedure is usually accomplished on an outpatient basis, and donors usually return promptly to their usual activities, requiring only oral analgesia.

Management after Transplant

All patients undergoing bone marrow transplantation require intense supportive care between the time that the hematopoietic progenitor cells are infused and when they are able to produce adequate numbers of granulocytes, platelets, and erythrocytes. Early after the transplant, therapy is focused on prophylaxis against infection, bleeding, and GVHD.

Table 10: Antimicrobial prophylaxis in allogeneic marrow transplant

Pathogen	Prophylaxis	Timing
Bacteria	Variable	By onset of neutropenia Until engraftment
Fungi	Fluconazole, 100 mg PO qd	Day - 7 to engraftment
Pneumocystis carinii	Bactrim-DS, 2 PO twice weekly	Engraftment to day ISO*
Viruses Herpes simplex	Acyclovir, 250 mg/m ² IVq 8 hr	Day - 1 to engraftment
Cytomegalovirus	Ganciclovir, 5 nig/kg twice weekly	Engraftment to day 100

*Or until immunosuppressive therapy is stopped.

In seropositive patients or recipients of seropositive marrow; it is best to use seronegative blood products in seronegative patients or to filter white cells from seropositive donors.

Blood components should be irradiated to avoid inducing GVHD mediated by lymphocytes from an HLA-incompatible donor. The average time to recovery of granulocyte counts greater than 500/ μ L is 10 to 20 days. Platelets are usually the slowest to recover.

Table 11: Complications of Allogeneic Bone Marrow Transplantation

Early complications	Late complications
<p>Regimen-related toxicity</p> <ul style="list-style-type: none"> ● Cystitis ● Mucositis ● Pulmonary complications ● Renal toxicity ● Neurologic toxicity <p>Venoocclusive disease of the liver</p> <p>Idiopathic pneumonia syndrome</p> <p>Graft failure</p> <p>Infection</p> <p>Immunodeficiency</p> <p>Acute graft-vs.-host disease</p> <p>Bleeding</p>	<p>Regimen-related toxicity</p> <ul style="list-style-type: none"> ● Cataracts ● Neurologic toxicity ● Gonadal toxicity ● Endocrine toxicity ● Abnormal growth and development <p>Immunodeficiency</p> <p>Infection</p> <p>Chronic graft-vs.-host disease</p> <p>Relapse of primary tumor</p> <p>Second malignancy</p>

Acute Graft-versus-Host Disease

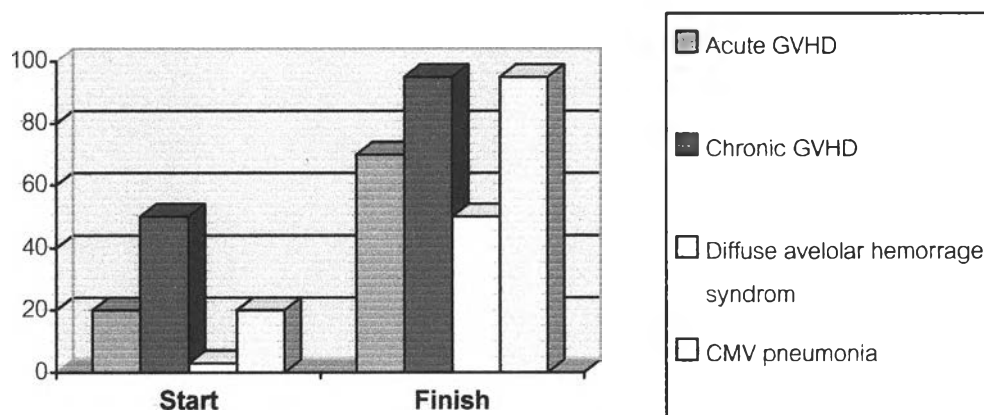
Even when the donor and host are completely matched at the HLA loci, there are usually differences between the donor and the host at minor histocompatibility loci. The infusion of functional lymphocytes from the donor into the host, whose cells express antigens perceived as foreign by the donor lymphocytes, results in the stimulation of an immune response in which donor CD4 + and CD8 + T cells and natural killer cells participate. The activated T cells and natural killer cells produce cytokines such as interferon γ and tumor necrosis factor α that are thought to mediate the tissue destruction

associated with acute GVHD. The disease is manifested by a skin rash, liver function test abnormalities, and diarrhea. Histologically, the skin disease is a lichenoid reaction, the liver shows bile duct inflammation, and the gastrointestinal tract shows inflammation of crypts and mucosal inflammation and sloughing. The onset of the disease is usually within the first 2 months post transplant. The severity of the disease is graded based upon the organ dysfunction. It is not clear why some organs are spared damage in this systemic immune response. In addition to the damage to the affected end organs, florid acute GVHD is associated with immunosuppression and susceptibility to infection.

Chronic GVHD

Although chronic GVHD may occasionally develop in the absence of acute GVHD, it is clear that the diseases are largely related. Chronic GVHD usually develops more than 3 months after transplant. It is characterized by skin rash, sclerodermatitis, alopecia, hepatic dysfunction, oral lichenoid lesions, and a sicca complex (dry eyes and mouth) and may involve obliterative bronchiolitis and gastrointestinal motility disorders. The disease is mediated by donor T cells, most of which are recognizing minor histocompatibility complex differences in the host. In addition, there may be autoreactive donor T cells that recognize a self-antigen shared by the donor and host, especially when there is tissue damage. The activated T cells produce a variety of cytokines, including interleukin (IL) 4, which has been suggested as a primary mediator of the disease. Apparently newly developed T cells in the adoptive host do not undergo normal negative selection to delete autoreactive cells and induce self-tolerance. Patients who had grade II or greater acute GVHD and those who are older are at increased risk.

Table 12: Timing of Major Complications of Bone Marrow Transplantation



Day after hematopoietic progenitor cell infusion

Infections

Infections that complicate allogeneic bone marrow transplantation are discussed.

Delayed Immune Recovery

After bone marrow transplantation donor stem cells attempt to recapitulate the ontogeny of the immune system. However, in adults, thymic involution often leads to inadequate generation of new T cells. The T cell function of the transplant recipient is dependent upon peripheral expansion of the relatively few T cells transferred with the marrow graft. T cell recovery after transplantation may take 18 months or more. The initial T cells detected in the peripheral blood are not fully functional, often failing to produce IL-2 upon stimulation. With time, normal T cell responses may develop; however, the use of live viral vaccines is to be avoided.

Graft Rejection

Rejection of a bone marrow graft in most cases represents destruction of the graft by functional host lymphocytes that survived the preparative regimen. This complication is most frequent in patients with aplastic anemia who do not receive total-body radiation therapy. Predisposing factors include previous blood transfusions (which sensitize the host), less intensive preparative regimens (which fail to kill host lymphocytes), and the removal of T cells from the allograft (donor T cells produce CSFs and may interfere with host cell rejection).

Tumor Recurrence

In general, tumor recurrence is an authentic recurrence of malignant cells of host origin. Although several approaches to this problem may be taken, the infusion of large numbers of donor T cells, obtained by leukapheresis or aspiration of buffy coat of donor blood, often induces complete remission in relapsed leukemia, particularly chronic granulocytic leukemia. Such donor T cells may also worsen GVHD. Experimental efforts to further improve the efficacy of donor T cells include the administration of IL-2 after transplant and immunizing the donor against the tumor before the transplant.

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