

## ผลสัมฤทธิ์ของการปลูกเซลล์ต้นกำเนิด

### จากหน่วยปลูกถ่ายไขกระดูกที่มีงบประมาณจำกัด

## Outcome of Stem Cell Transplantation from Low resources set up Bone Marrow Transplantation unit

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### บทคัดย่อ

ปัจจุบันแม้จะมีความก้าวหน้าในการดูแลผู้ป่วยกลุ่มโรคมะเร็งมากขึ้นในประเทศไทย แต่ยังมีผู้ป่วยบางส่วนที่ไม่ตอบสนองต่อการรักษาในระดับมาตรฐาน ทำให้เกิดการกลับเป็นซ้ำของโรค อีกทั้งยังเป็นภูมิภาคที่มีโรคทางพันธุกรรม เช่น โรคเลือดธาลัสซีเมียเป็นจำนวนมาก อันเป็นภาระค่าใช้จ่ายในระบบสาธารณสุขไทย

การปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด ถือเป็นการรักษาที่ได้ผลและหายขาดได้ในกลุ่มผู้ป่วยโรคมะเร็ง โรคเลือดธาลัสซีเมีย โรคไขกระดูกฝ่อรุนแรง และอื่นๆ

การศึกษานี้ รายงานถึงผลสัมฤทธิ์ของการทำการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดทั้งแบบที่ใช้เซลล์ต้นกำเนิดจากผู้ป่วยและแบบที่ใช้เซลล์ต้นกำเนิดจากพี่น้อง แก่ผู้ป่วยกลุ่มโรคต่างๆ จำนวน 13 ราย ค่ากลางของระยะเวลาในการติดตาม 11 เดือน (2 เดือน – 47 เดือน) ค่าการอยู่รอดโดยรวมเป็น 100% ค่ากลางของระยะเวลาปลอดโรคคิดเป็นระยะเวลาเฉลี่ย 10 เดือน พบภาวะแทรกซ้อนเซลล์ต้นกำเนิดใหม่ต้านร่างกายผู้ป่วยแบบเฉียบพลันขั้นที่ 1 หนึ่งราย โดยไม่พบภาวะแทรกซ้อนแบบเรื้อรัง ค่ากลางของค่าใช้จ่ายในการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดชนิดใช้เซลล์ต้นกำเนิดของผู้ป่วยคิดเป็น 371,000 บาท (245,000 – 520,500 บาท) และชนิดใช้เซลล์ต้นกำเนิดจากพี่น้องคิดเป็น 530,300 บาท (483,300 – 592,000 บาท) ซึ่งพบว่าค่าใช้จ่ายถูกกว่าการปลูกถ่ายเซลล์ต้นกำเนิดแบบเดียวกันในประเทศพัฒนาแล้วอีกหลายประเทศ อีกทั้งปลอดภัยและมีการใช้ทรัพยากรอย่างมีประสิทธิภาพ นอกจากนี้การคงไว้ซึ่งสิ่งจำเป็นพื้นฐานในการปลูกถ่ายเซลล์ต้นกำเนิด เช่น ระบบกรองอากาศด้วย HEPA filter และห้องอัดแรงดันบวก สามารถลดปัญหาค่าใช้จ่ายอันเกิดจากผลข้างเคียงของการทำการปลูกถ่ายเซลล์ต้นกำเนิดได้

**คำสำคัญ:** การปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือด, ทรัพยากรที่มีจำกัด

## ABSTRACT

In Thailand, despite the improvement of care for malignancies, some groups of patients have failed to respond to standard treatment and faced recurrence of diseases. Thailand is an endemic area of several genetic disorders and thalassemia has been a budgetary burden for the Royal Thai government.

Hematopoietic stem cell transplantation (HSCT) is a definite cure for several hematological diseases including malignancies, thalassemia and severe aplastic anemia. Bone marrow transplantation (BMT) was found promising in spite of low resources. Thirteen cases of BMT (10 cases for autologous and 3 cases for allogeneic transplantations) were performed and outstanding outcomes were reported in this study. The median follow-up time was 11 months (2 months – 47 months range). Both disease-free survival and overall survival were 100% with 10 months median disease-free survival time. One case had acute GVHD grade I with no evidence of chronic GVHD. Moreover, the median cost of autologous BMT was US\$10,601 dollars (US\$7,113 – 14,872 range) and the median cost of allogeneic BMT was US\$ 15,153 dollars (US\$ 13,808 – 16,924 range) which were more economical than the BMT costs in the developed countries. Maintaining basic necessities such as HEPA filter system with positive pressure gradients room air and lab checkup as much as necessary can both reduce expenses and prevent complications.

**Keyword:** Stem Cell Transplantation, Low resources set up Bone Marrow Transplantation

Pediatric cancer is a challenging field of medicine because of its own diagnosis and therapeutic procedure combined with emotional burden often related to financial, educational, cultural and human resources.<sup>(1)</sup>

In Thailand, thalassemia is the most common gene-related hematologic disease. Approximately 40% of the Thai population carry thalassemia traits and about 1% manifest the disease.<sup>(2)</sup> It accounts for a significant proportion of childhood morbidity and related health care expenses.<sup>(3, 4)</sup> In spite of major advances in supportive care during the past decade,<sup>(5)</sup> many patients in Low and Middle Income Countries (LMICs) still managed poorly because of treatment costs and lack of accessibility to proper medical treatment.

Even though bone marrow transplantation offers a maximal chance of cure for the majority of blood cancer patients, it is complicated and demands great efforts, budget and resources beyond the hospital extent.

A project to set up a unit of bone marrow transplantation (BMT) with low resources in the Regional Cancer Center in the South-Eastern area of Thailand was initiated to offer transplantation. Sunpasitthiprasong Hospital collaborated with the Department of Pediatric Hemato-Oncology, Mahidol University in the project. The collaboration was to ascertain transplantation in compliance with the international standard and to offer training program, donor care, stem-cell manipulation and transplantation process. One of the primary aims of the project was also to evaluate feasibility, outcomes and costs of BMT under low resources.

The purpose of this paper is therefore to report on the effectiveness and costs of the BMT in a unit with low resources.

## Material & Methods

Due to the fact that BMT offered in medical centers under the social healthcare system is supported by neither social welfare nor any foundations, setting

up a BMT unit has to be sponsored by other sources. Moreover, laboratory procedures and costs such as to cyclosporine a blood level, to monitor CMV reactivation, and to analyze flow cytometry and chimerism depend on individual cases and types of transplantation.

To support the BMT unit with low resources of the project under this study, Ramathibodi hospital at Mahidol university contributed to the BMT unit setup, standardization and academic matters. The processes of setting up covered the following aspects:

- Technical and professional assistance such as BMT unit location, size, design, infection control issues and most importantly the system of transplantation
  - A 4-beds unit modified from a special ward (2 beds with positive pressure gradients and centralized high efficacy particulate air (HEPA) filtration system; the other 2 beds with private bath room and split air conditioning system for high risk patients such as severe neutropenic malignancies) and enforcement of strict hand wash
  - Training and essential drug supplies for the team and staff
  - Blood bank, a collection of stem cells stored at minus 60 degrees Celsius, and various irradiated blood component from high energy linear accelerated blood irradiator
  - Apheresis machine to harvest stem cells from donor advantageous to plasmapheresis in indicated patients such as Guillain-Barre syndrome, thrombotic thrombocytopenic purpura, acute renal failure etc.

In the first phase, autologous BMT was performed by using patient's own bone marrow for treating cancers such as relapsed lymphoma, multiple myeloma and neuroblastoma. Thereafter, allogeneic BMT using bone marrow of donor with compatible Human Leucocytes Antigen (HLA) matching was performed.

All HSCT patients were treated in positive-pressure isolation rooms and received antibiotics to

prevent *Pneumocystis carinii* pneumonia, cytomegalo virus, and Epstein-Barr virus. The criteria of engraftment are an absolute neutrophil count more than  $0.5 \times 10^9$  cell/L for three consecutive days or a platelet count more than  $20 \times 10^9$ /L without transfusion for seven consecutive days.<sup>(6,7)</sup>

## Results

A total of 13 patients had successful engraftment and were evaluated for the costs of the procedure, focusing on the inpatient costs till discharged from the hospital. Table 1 demonstrates transplantation characteristics of patients, conditioning regimens and post-BMT complications.

**Table 1:** Transplantation characteristics of patients, conditioning regimens and post-BMT complications

Total patient (n = 13)	
Male	3 (23.1%)
Female	10 (76.9%)
Mean age in years (range)	27 (5 – 58)
Median duration of hospitalization in days (range)	43 (30 – 60)
Type of transplant	
Autologous	10 (76.9%)
Allogeneic (HLA matched sibling donor)	3 (23.1%)
Diagnosis	
Thalassemia	2 (15.4%)
Relapsed lymphoma	2 (15.4%)
Relapsed acute lymphoblastic leukemia	1 (7.4%)
Neuroblastoma stage III	2 (15.4%)
Relapsed/high risk multiple myeloma	6 (46.1%)
Conditioning regimens	
Busulfan/Cyclophosphamide	1 (7.7%)
Busulfan/Fludarabine/ATG	2 (15.4%)
Busulfan/Melphalan	2 (15.4%)
Melphalan	6 (46.1%)
Melphalan/BCNU/Etoposide	2 (15.4%)
Complications	
Acute GVHD	
gr I	1
gr II - IV	0
Chronic GVHD	
	0
Hemorrhagic cystitis	1

\*GVHD = Graft Versus Host Disease

The majority of the transplantations were autologous and most of the diseases were hematologic malignancies (2 recurrent Hodgkin lymphoma, 2 recurrent neuroblastoma and 5 recurrent multiple myeloma). The overall and disease free survival was 100% for both types of transplantation.<sup>(8)</sup> The period of cost was calculated from the day of admission for transplantation to the day of discharge. The median duration of hospitalization were 43 days (30 – 60 days).

Post-BMT complications were only acute graft

versus host disease (GVHD) grade I in 1 case, hemorrhagic cystitis from BK virus in 1 case and low grade oral mucositis in some cases. The median total cost of bone marrow transplantation was US\$10,601 (US\$7,113-14,872 range) for autologous and US\$15,153 (US\$13,808–16,924 range) for allogeneic type as shown in Table 2. The comparison of costs of BMT with other countries was shown in Table 3. Details of hospital charges in each category were illustrated as mean in Table 4.

**Table 2:** Costs of autologous and allogeneic bone marrow transplantation

Type of transplant	Number of patients (n=13)	Average Age years (range)	Median time of hospitalization days (range)	Median total cost US Dollars (range)
Autologous	10 (76.9%)	32.6 (5 – 58)	41 (33 – 60)	10,601 (7,113 – 14,872)
Allogeneic	3 (23.1%)	8.3 (5 – 12)	51 (46 – 57)	15,153 (13,808 – 16,924)

**Table 3:** Comparison of costs of autologous and allogeneic bone marrow transplantation in some main countries and Thailand

	USA <sup>(8,9)</sup> US \$	France <sup>(10,11)(a)</sup> US \$	India <sup>(12)(c)</sup> US \$	Thai (centre) <sup>(13)</sup> <sup>(b)</sup> US \$	Thai (SPS) <sup>(c)</sup> US \$
Autologous BMT	51,312	11,031	12,500	25,550	10,601
Allogeneic BMT	105,300	78,700	17,914	23,882	15,153

(a) Total 60 d. post BMT (b) Total 1 yr. post BMT (c) Timing Admit until discharge

**Table 4:** Other hospital charges

	US\$	%
Accommodation	825	7.2
Blood product and transfusion charges include stem cell harvest and infusion	2,665	23.2
Pharmacy	5,662	49.3
Investigation (labs, X-ray)	932	8.1
Equipment and medical devices	456	4.0
Procedure	212	1.8
Medical consultation	680	5.9
Miscellaneous (including consumables, catheter, O <sub>2</sub> )	50	0.4
	11,482	100%

## Discussion

BMT is a curative treatment for hematologic diseases and high risk malignancies which poorly respond to standard treatment especially chemotherapy. Up to date it has been the only definitive cure for severe thalassemia disease with reported consistent thalassemia-free survival rate of over 80% in selected young low-risk patients who received BMT with HLA match-related donor<sup>(15)</sup> and life improvement program.<sup>(16-17)</sup> In the area where thalassemia is endemic such as the South-Eastern area of Thailand, there has been a severe shortage of center for BMT. This is not only due to a lack of financial resources, but also a lack of subspecialty expertise in this field and especially a perception that setting up a BMT center is highly complex and expensive. In fact, BMT treatment is less expensive than the cost of long-term supportive care for patients with severe thalassemia.<sup>(18)</sup>

In this study, it was found that appropriate BMT unit with low resources could be set up with support from its surrounding organizations. Once the unit was established with medical standards, BMT could offer high chances of disease-free survival.

Outcomes of BMT in the unit with low resources were comparable to those with high resources in the developed countries and the cost was affordable. Although HEPA filtering and positive pressure gradients system is important to decrease adverse events, we found only low grade complications such as acute GVHD gr I, oral mucositis, acute diarrhea and BK viral urinary tract infection.<sup>(19)</sup> In terms of cost, it may be difficult to compare with other sites of various conditioning protocols, use of GVHD prophylaxis, differences in supportive physician's discretion in using the available resources, and differences in periods of follow-up treatment including various investigations. However, Thai patients are less likely to be able to afford the high cost of the transplantation between US\$30,000 and US\$88,000 for a single autologous

transplantation and US\$200,000 or more for a matched unrelated myeloablative allogeneic procedure in Europe and USA.<sup>(20-22)</sup> Even though the cost of the transplant in developing countries is much lower than overseas transplantation,<sup>(23-24)</sup> many patients in Thailand cannot afford it due to their low socio-economic background and a lack of sufficient insurance coverage and governmental support.

## Conclusion

The findings in the effectiveness and cost of BMT in a unit with low resources in this study may set a useful precedent to extent access for bone marrow transplantation in lower to middle income regions. A BMT unit with low resources can be appropriately set up and the effectiveness of treatment is in accordance with safety standards for both autologous and allogenic BMT.

Consequently, more BMT centers should be established as they contribute not only to advancement in the cure of both malignant and non-malignant diseases, but also to empowerment of tertiary medical care in the unserved area and multidisciplinary team work. More significantly, recent publication has demonstrated that the budget for related HSCT thalassemia patient was more cost-effective and reducing more government expenditures than blood transfusion combined with iron chelation therapy.<sup>(25)</sup>

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