Outcomes of Total Body Irradiation-Based Myeloablative Conditioning Regimen for Allogeneic Stem Cell Transplantation in Pediatric Leukemia

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Background: *The total body irradiation (TBI)-based myeloablative conditioning regimen for allogeneic stem cell transplantation has been developed to overcome treatment failure and to improve overall survival of pediatric leukemia. The present study retrospectively reports the safety and success of this treatment regimen.*
Objective: *The objective was to report the safety and success of this treatment program based on the evaluation of effectiveness and complications from treatment, overall and disease free survival rate of patients and prognostic factors that might affect survival outcome.*
Material and Method: *Forty-four pediatric leukemic patients received the TBI-based myeloablative conditioning regimen for allogeneic stem cell transplantation at Ramathibodi Hospital between 1997 and 2011. The data were evaluated for clinical outcome.*
Results: *With the median follow-up period at 5.9 years (ranging from 0.3 to 16.7 years), 29 cases (65.9%) were alive, 15 cases (34.1%) died. The Kaplan-Meier estimated that the overall survival rate was 72.5% after three years, 70% after five years, and 63.0% after 10 years. The diseases free survival rates at 3, 5 and 10 years were 85.5%, 82.5%, and 82.5%, respectively. Significantly, lower survival rate was observed in patients with relapsed disease prior to transplantation and in patients with no remission of disease after transplantation.*
Conclusion: *The TBI-based myeloablative conditioning regimen for allogeneic stem cell transplantation can be applied to management of selected pediatric leukemic patients.*

Keywords: *Total body irradiation, Myeloablative conditioning regimen, Allogeneic stem cell transplantation, Pediatric leukemia*

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Leukemia is the most common hematological pediatric malignancy. Good remission and long-term disease-free survival can currently be achieved by effective chemotherapy regimen. However, relapse of the disease could occur after treatment completion, leading to poor survival outcome. This is problematic, especially in patients categorized in high-risk group (less than 1 year of age or more than 10 years old, initial white blood cell count more than 50,000 cells per cubic millimeter, Philadelphia chromosome positive, central nervous system or testicular involvement at initial diagnosis), or patients with relapsed acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). Hematopoietic stem cell transplantation has been considered as a curative intent or salvage therapy to improve patients' survival[1-3]. At Ramathibodi Hospital, the total body irradiation (TBI)-based myeloablative conditioning regimen for allogeneic stem cell transplantation has been developed in 1997. The development of this technique was aimed to provide sufficient immunosuppression to avoid rejection and

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allow engraftment of donor hematopoietic/immune cells. Another main purpose was to eradicate all malignant cells by chemotherapy and radiotherapy. This treatment was designed for management of patients in high-risk group or patients with relapsed ALL, AML, and CML.

The objective of the present retrospective study was to report the safety and success of this treatment program based on the evaluation of:

1) effectiveness and complications from treatment,

2) overall and disease-free survival rate of patients,

3) prognostic factors that might affect survival outcome.

Material and Method

The present study was approved by the Ethical Clearance Committee on Human Rights related to Researches Involving Human Subjects, Mahidol University (protocol number ID 04-54-01). The patients' medical record files were collected between 1997 and 2011 for evaluation of the results. Forty-four available patients data were included in the TBI-based myeloablative conditioning regimen for allogeneic stem cell transplantation.

Histocompatibility

All patients and donors must be verified that their human lymphocyte antigen (HLA) class I serologic typing and HLA class II DNA typing matched before the treatment. The histocompatibility tests were performed at Department of Pathology, Faculty of Medicine Ramathibodi Hospital. Lymphocyte cytotoxic test (LCT) or sequence specific oligonucleotide (SSO) test were used to detect antigen or allele of human leukocyte antigen (HLA) class I, whereas sequence specific primer (SSP) test was used to determined HLA class II. Normally, six loci or ten loci were tested for related or unrelated donors, respectively, and matched donors meant that they had 6/6 or 10/10 matched with recipients.

The stem cell sources

The stem cell sources of these patients were harvested from peripheral blood stem cell, bone marrow of donors, and cord blood stem cell.

Conditioning and conditioning related regimen

The conditioning regimen consisted of cytarabine 3 g/m^2, cyclophosphamide 45 mg/kg, mesna 15 mg/kg, and TBI 200 centrigray (cGy) twice daily (bid) for three consecutive days (total dose 1,200 cGy). The TBI technique had been performed by lateral opposed field in supine position (or in bent knees position if the length of the body extended over the maximum treatment field size) using 6-megavoltage (MV) photon with 350 cm source-skin distance (SSD). Radiation dose was prescribed at the midline of the body with the dose rate of 0.09 cGy/monitor unit (MU). This radiation technique was confirmed to provide the uniformity of radiation dose distribution throughout the whole body of all patients calculated with mean difference value of -3.2 + 2.5% from the prescribed dose (The International Atomic Energy Agency (IAEA) acceptance in which the uniformity of dose distribution throughout the body in TBI must be maintained within $\pm$10% of the prescribed dose)[4] while retaining as low as reasonably achievable dose to organs at risk (lungs, liver, kidneys, urinary bladder, and brain for patients having previously received cranial irradiation) to avoid severe late complications[5]. The conditioning related regimen consisted of ranitidine and dexamethasone eye drop. Both ranitidine and dexamethasone eye drop were started approximately two weeks prior to the transplantation date; ranitidine was continued until 12 days after transplantation. Granulocyte stimulating factors (G-CSF) was started one day after the transplantation date and continued for 12 days.

Transplantation date

To minimize febrile neutropenia risk, the transplantation date was set within one week after having completed TBI.

Graft versus host disease (GVHD) prophylaxis

GVHD prophylaxis was composed of cyclosporin A 3 mg/kg/day and methotrexate 5 mg/m^2 started two days prior to transplantation date and continued for 12 days after with methotrexate being continued only on day 1, 3, 6, and 11 after transplantation.

Treatment schedule

The detail of treatment protocol is shown in Fig. 1.

Chimerism analysis

Chimerism analysis was monitored from engraftment and every two weeks during the first 100 days after stem cell transplantation, using variable number of tandem repeats analyses (for donor- recipient sex match) and fluorescein in situ hybridization for

Patient's name: HN. Age ปี Sex. Bl.gr. DOB Dx.
BW kg. Ht cm BSA. m^2 Donor HN. DOB : Sex Bl.gr.

Day	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12
Conditioning Regimen																					
- Ara-c (3 g/m^2) = mg IV Q 12 hr x 6 doses		x	x	x	x																
- CTX (45 mg/kg) = mg IV x 2 doses			x	x																	
- Mesna (15 mg/kg) = mg IV at hr 0, 3, 6, 9,12			x	x																	
- TBI						x	x	x													
Antibiotic Prophylaxis																					
- Ciprofloxacin = mg PO BID PC	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
- Penicillin V = mg PO QID AC & HS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
- Itraconazole = mg PO BID									x	x	x	x	x	x	x	x	x	x	x	x	x
- Acyclovir = mg PO TID PC	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Conditioning related regimen																					
- Ranitidine = mg PO BID	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
- Dexamethasone eye drop 2 gtts both eyes QID	x	x	x	x																	
- G-CSF (5 mcg/kg) = mcg IV QD										x	x	x	x	x	x	x	x	x	x	x	x
GVHD Prophylaxis																					
- Cyclosporin A (3 mg/kg/day) = mg IV Q 12 hr							x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
- MTX (5 mg/m^2) = mg IVP										x		x			x					x	

Fig. 1 MRD BMT for Hematologic Malignancies (RAMABMT 001).

X and Y chromosomes (for donor- recipient sex mismatch).

Complications from treatment

Acute complications were defined as those occurred during the period of treatment scheduled up to three months after treatment completed. The late complications were defined as those occurred later than the third month after treatment. The acute and late complications were evaluated and managed.

Post transplantation follow-up schedule

The detail of follow-up schedule was shown in Fig. 2. Any abnormality detected was determined and managed according to each medical specialist.

Definition and statistical analysis methods

Successful engraftment

Successful engraftment was defined by the following criteria: 1) neutrophil engraftment, referred to an absolute neutrophil count, of greater than or equal to 500/mm^3 for three consecutive days, 2) platelet engraftment, referred to a platelet count, of greater than or equal to 20,000/mm^3 for three consecutive days and without transfusion for seven days, 3) erythroid engraftment, referred to a hematocrit level, of 25% or greater for at least 20 days without transfusion. In practice, if successful neutrophil engraftment were achieved, successful platelet and erythroid engraftment would often be followed. Failure engraftment for myeloablative transfusion was defined by the lack of neutrophil recovery at 28 days after stem cells infusion[6].

Remission of disease

Remission of disease after transplantation was evaluated by patient's clinical status and CBC along with engraftment analysis by chimerism-testing on engraftment date and on the thirtieth, sixtieth, and one hundredth day after engraftment date by either DNA fingerprint (same sex donor) or FISH for XX, XY (different sex donor)[7].

Graft versus host disease (GVHD)

GVHD was diagnosed mainly from clinical manifestations of each organ involved according to accepted criteria. Traditionally, clinical GVHD occurring within 100 days after transplantation was called acute

Tissue/Organ/Test	6 M	1 Y	Annually
Immunity			
- Pneumocystis carinii pneumonia prophylaxis	✓		—
- Diphtheria-pertussis-tetanus, hepatitis B viral, inactivated polio and pneumococcal vaccine Immunization		✓	
Oral			
- Dental assessment	✓	✓	$\overline{q}$ 6 M
Liver			
- Liver function teat	✓	✓	✓
- Ferritin		✓	✓
Respiratory			
- Pulmonary function test		×	
- Chest radiography	A	A	A
- Smoking tobacco avoidance	✓	✓	✓
Endocrine			
- Thyroid function test		✓	✓
- Growth velocity in children		✓	✓
- Gonaldal function assessment (prepubertal men and women)	✓	✓	✓
- Gonadal function assessment (prepubertal men and women)		✓	✓
Ocular			
- Ocular clinical Symptom evaluation	✓	✓	✓
- Schirmer testing	C	C	C
- Ocular fundus exam		✓	A
Skeletal			
- Bone density		✓	A
Second cancers			
- 2nd cancer vigilance counseling		✓	✓
- Breast/skin/testes self-exam		✓	✓
- Pap smear/mammogram (over age 40)		✓	✓
Nervous system			
- Neurologic clinical evaluation		✓	A
Kidney			
- BP	✓	✓	✓
- Urine protein	✓	✓	A
- BUN, Cr.	✓	✓	✓
Vascular			
- Cardiovascular risk factor assessment		✓	✓
Psychosocial			
- Psychosocial/QOL clinical assessment	✓	✓	✓
- Sexual function assessment	✓	✓	✓

✓ = All patient; × = Allogenic patient; A = Abnormal testing; C = chronic GVHD

Fig. 2 Long-term survivor follow-up post hematopoietic cell transplantation.

GVHD while that occurring after 100 days was called chronic GVHD[8].

Statistical analysis methods

SPSS Statistic version 17.0 was used for the estimation of Kaplan-Meier curve for overall and disease-free survival. The overall and disease-free survival rates were determined from the transplantation date until date of last visit. Patient status, dead or alive, was for overall survival while disease status, in

remission or not, was for disease free survival. The log-rank test was used for estimating factors related overall survival. A *p*-value less than 0.05 was regarded as statistically significant.

Results

The data analysis was based on 44 cases. There were 25 males (56.8%) and 19 females (43.2%) with the mean age of 9.3±3.9 years (ranging from 2 to 15 years old) when received TBI-based myeloablative regimen. The stem cell sources were harvested from peripheral blood stem cell in 18 patients, the rest from bone marrow of donors; only one patient used cord blood stem cell. Nine patients with no recorded data were excluded. The median infused stem cells were 7.34 (1.08 to 8.00) million cells per recipients' weight (kilogram).

The median of follow-up period was 5.9 years (ranging from 0.3 to 16.7 years). At the time of transplantation, seven cases (15.9%) showed ALL high-risk in first remission (CR1), 13 cases (29.5%) with ALL relapsed disease in second remission (CR2), 14 cases (31.8%) with AML in first remission (CR1), three cases (6.8%) with AML relapsed in second remission (CR2), and seven cases (15.9%) with CML chronic phase. Successful engraftment was observed in 43 cases (97.0%). The median times of neutrophil and platelet engraftment were 16 and 28 days post transplantation, respectively.

The details of complications were shown in Table 1. Most common acute complication was low grade fever[9]. No acute complication related death was recorded. The most common late complication was hypogonadotropic hypogonadism[10]. At the time of the present report, 37 cases (84.0%) were in remission, and seven cases (15.9%) showed relapse of the disease. Regarding to the status of patients, 29 cases (65.9%) were alive and 15 cases (34.1%) were dead (10 cases were diagnosed CR2 status before transplanted). The causes of deaths were defined as shown in Table 2.

The Kaplan-Meier estimates of 3, 5, and 10-year overall survival rates for all patients were approximately 72.5%, 70.0%, and 63.0%, respectively. Based on the analysis, the highest death rate was observed within the first year after treatment. However, after one year, the death rate remained at 63.0% for eight years. The data analyses revealed the overall survival continued to approximately 15 years of the follow-up period with less than 50% death rate. As shown in Fig. 3, 4, the mean overall survival rate of this treatment was 11.3 years (95% CI 9.1 to 13.5) with the disease-free survival rate at 3, 5, and 10 years were 85.5%, 82.5%, and 82.5%, respectively. The disease-free survival rate remained unchanged at 82.5% for another four years. The mean disease-free survival was around 14.0 years (95% CI 12.1 to 15.8). The longer disease-free survival rate could be explained by the causes of patient's death that were not related to the disease.

Table 1. Acute and late complications from treatment

Acute complications	Events* n = 72 (100%)
Low grade fever	44 (100.0)
Acute graft versus host disease (less than grade 3)	19 (8.4)
Acute cystitis	5 (2.2)
Acute pulmonary infection	3 (1.3)
Typhlitis	1 (0.4)
Late complications	**Events* n = 55 (100%)**
Hypogonadotropic hypogonadism	17 (7.5)
Osteopenia	11 (4.8)
Chronic graft versus host disease (score 1)	8 (3.5)
Cataract	8 (3.5)
Hypothyroidism	4 (1.8)
Veno occlusive disease of liver	2 (0.9)
Secondary malignancy	2 (0.9)
Constrictive lung disease	1 (0.4)
Chronic cystitis	1 (0.4)
Impaired renal function	1 (0.4)

Table 2. Causes of death

Causes of death	Cases
Relapsed disease	5
Infections (pulmonary aspergillosis 2 cases, *E. coli* septicemia 1 case, Herpes encephalopathy 1 case, Unknown organism 1 case)	5
Anaplastic astrocytoma	1
Acute respiratory distress syndrome	1
Hepatorenal syndrome	1
Brain edema	1
Traffic accident	1

* Events mean the outcomes that detected from treatment, some patients had more than one event

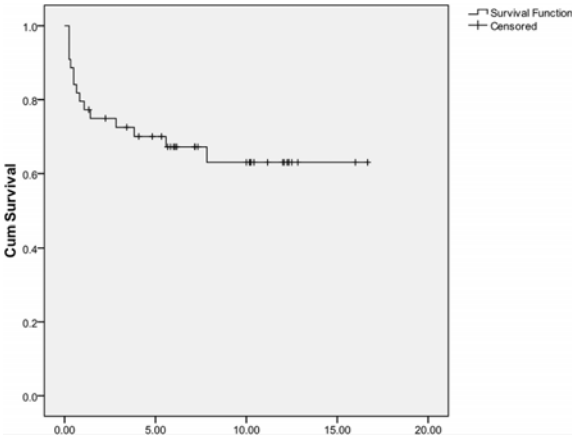

Fig. 3 Overall survival (year).

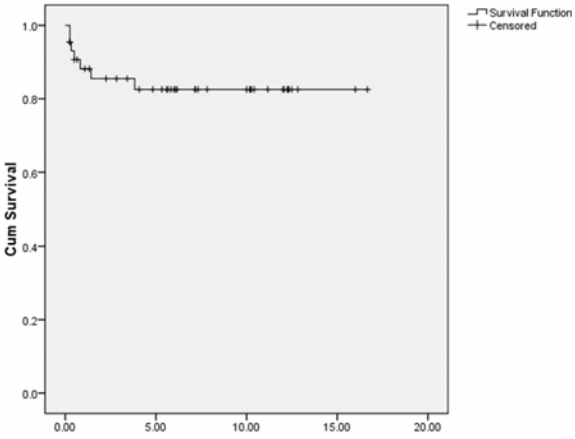

Fig. 4 Disease free survival (year).

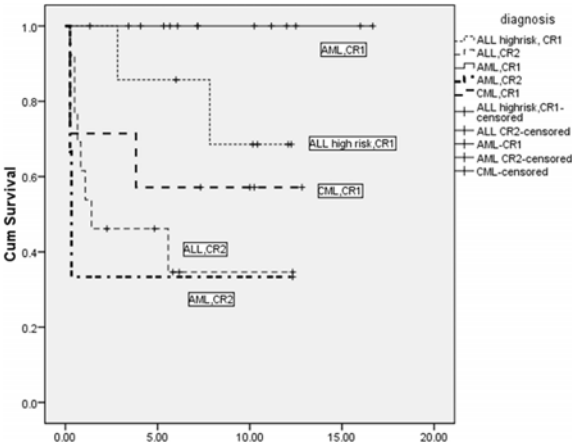

Fig. 5 Overall survival (year) and diseases.

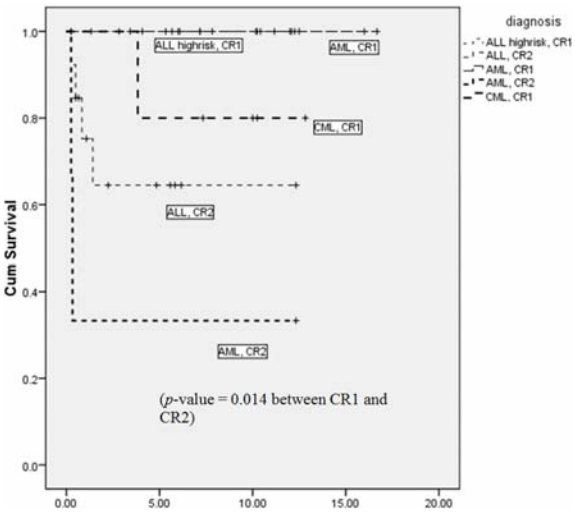

Fig. 6 Disease free survival (year) and diseases.

The overall survival rate of each disease characteristic was illustrated in Fig. 5. Patients with relapsed diseases (CR2) before transplantation showed significantly lower overall and disease-free survival rates than patients with remission diseases (CR1), (*p*-value = 0.004 and 0.014, respectively). After transplantation, the remission of disease was the prognostic factor that associated with survival outcome. For patients with diseases in remission after treatments, the 5-year overall survival rate was 94.7% and continued at 90% after 5.5 years. In comparison to patients without diseases in remission after treatment, the overall survival rate was significantly different (*p*-value <0.0001).

Discussion

Previous treatment of pediatric leukemia with TBI at Ramathibodi Hospital was based on a single fraction of 9 to 10 Gy. However, due to severe late complications observed, modified dose delivery was adjusted[11]. Even though the total dose of TBI regimen was optimized, the number and type of fractionation remains controversial. The total radiation dose of 12 Gy in six fractions of TBI is widely used for myeloablative effects; yet, this treatment still spares severe late complications and gain benefit of engraftment[11-17].

According to radiobiology, leukemias have long been considered as radiosensitive tumors with minimal or no capacity for repair of radiation damage. The TBI radiotherapy treatment for leukemias was endorsed by "5Rs of radiobiology". Leukemic cell line sensitively responds to low dose radiation from high alpha/beta ratio. The hyperfractionation regimen with

very short period of overall TBI treatment time could overcome the effect of repopulation and repair sublethal damage of tumor cells. In addition, patients would also gain the benefit from reoxygenation and redistribution of tumor cells while normal tissue could be repaired sublethal damage from radiation during the treatment gap, leading to the reduce in life-threatening late complications (pneumonitis with lung fibrosis, chronic nephritis, and veno-occlusive liver disease)[11,15-18]. However, TBI-containing preparative regimen could cause potential late side effects such as cataracts, lung, liver toxicity, and long-term endocrine dysfunctions. These disadvantages should be considered in all patients during follow-up period[1,2,19-21].

Multiple clinical studies have been shown that TBI-based transplant conditioning regimens are associated with comparable or lower risk of relapse when compared to chemotherapy-only regimens for pediatric leukemia, especially for ALL. TBI-based transplant conditioning regimens has been considered as the treatment of choice[1,3,22-26].

This retrospective study highlighted the success of engraftment with long-term overall and disease-free survival rate for pediatric leukemic patients who received this TBI-containing preparative regimen. Because the compatibility of HLA class I or II of sibling donor and recipient have been verified as the important factor responsible for GVHD and relapsed disease[27]. To control this factor, all patients and donors in the present study must be confirmed that their HLA matched before treatment to achieve the best treatment outcome. The data analyses suggested that the patients with CR1 before transplantation and the remission of disease after transplantation were those with prolonged survival. The present study suggests that any leukemic patient without standard risk ALL presented at the time of the first diagnosis should be considered for receiving stem cell transplantation (if available), after complete standard treatment course to gain long-term survival benefit.

During the past decade, many studies evaluated TBI-based myeloablative conditioning regimen for allogeneic stem cell transplantation of pediatric leukemia. However, the clinical outcomes of these studies were found to be diverse in patient and disease characteristics, treatment regimens, and programs, final outcome status when reported and duration of follow-up[26,28-33]. We, therefore, could not compare the results of the present study to the previously reported outcome. Nonetheless, we chose the worldwide data of 5-year overall survival rate of allogeneic sibling donor transplantation from the Center for International Blood and Marrow Transplantation Research (CIBMTR) and the National Marrow Donor Program (NMDP)[34] as the reference. With only 44 cases evaluated in the present study, the 5-year overall survival rate is comparable to this reference.

Even though the present study suffered from small number of cases assessed and missing several details of patients' data, the study was compensated by long duration of follow-up period, which could suggest long term overall and disease-free survival rates. However, a larger number of cases is still required for evaluation of treatment effectiveness and long-term survival, which would include quality of life for these patients, in the future.

Conclusion

TBI-based myeloablative conditioning regimen for allogeneic stem cell transplantation could provide long term overall and disease-free survival rate for pediatric leukemic patients.

What is already known on this topic?

The allogenic stem cell transplantation for high-risk pediatric leukemia has been established as a curative treatment during the past several decades. Many factors related treatment outcome have been improved to cope with the longer-term successful treatment results. In Thailand, this treatment method was introduced in 1992 in much heterogeneity of pediatric hematologic diseases and a limited number of patients. The study has been continued with the improvement of treatment procedure to prolong disease free and overall survival of patients.

What this study adds?

This is the first report of clinical outcome of TBI-based myeloablative conditioning regimen for allogenic stem cell transplantation in pediatric leukemia in Thailand. The strength of this paper is the collected patients' data for only one disease (pediatric leukemia) with long-term follow-up period for treatment outcome.

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Potential conflicts of interest

None.

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ผลการรักษาผู้ป่วยมะเร็งเม็ดเลือดขาวในเด็กโดยการฉายรังสีทั้งตัวร่วมกับเคมีบำบัดและการเปลี่ยนถ่ายสเต็มเซลล์

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ภูมิหลัง: การฉายรังสีทั้งตัวร่วมกับเคมีบำบัดและการเปลี่ยนถ่ายไขกระดูกได้ถูกพัฒนาเพื่อเอาชนะความล้มเหลวของการรักษาและเพิ่มการรอดชีวิตของผู้ป่วยมะเร็งเม็ดเลือดขาวในเด็ก การศึกษาย้อนหลังนี้ได้รายงานความปลอดภัยและความสำเร็จของการรักษาด้วยวิธีการดังกล่าว

วัตถุประสงค์: รายงานความปลอดภัยและความสำเร็จของการรักษาโดยประเมินจากประสิทธิภาพ, ผลข้างเคียง, อัตราการรอดชีวิต, อัตราปราศจากโรค รวมถึงปัจจัยที่อาจจะมีผลต่อการรอดชีวิตของผู้ป่วย

วัสดุและวิธีการ: รวบรวมข้อมูลผู้ป่วยมะเร็งเม็ดเลือดขาวในเด็กที่ค้นหาได้จำนวน 44 ราย ตั้งแต่ พ.ศ. 2540 ถึง พ.ศ. 2554 ที่ได้รับการรักษาโดยการฉายรังสีทั้งตัวร่วมกับเคมีบำบัดและการเปลี่ยนถ่ายไขกระดูกเพื่อนำมาประเมินผลการรักษาทางคลินิก

ผลการศึกษา: จากช่วงเวลากลางของการติดตามผู้ป่วย 5.9 ปี (ระยะเวลาตั้งแต่ 0.3 ถึง 16.7 ปี) ผู้ป่วย 29 ราย (65.9%) ยังมีชีวิตอยู่ผู้ป่วย 15 ราย (34.1%) เสียชีวิตการประเมินโดย Kaplan-Meier พบอัตราการรอดชีวิตโดยรวมที่ 3, 5 และ 10 ปี เท่ากับ 72.5%, 70.0% และ 63.0% ตามลำดับ อัตราปราศจากโรคที่ 3, 5 และ 10 ปี เท่ากับ 85.5%, 82.5%, และ 82.5% ตามลำดับ ปัจจัยที่มีผลอย่างมีนัยสำคัญที่ทำให้การรอดชีวิตต่ำคือโรคเป็นกลับซ้ำก่อนเปลี่ยนถ่ายฯ และโรคที่ไม่หายขาดหลังการเปลี่ยนถ่ายฯ

สรุป: วิธีการฉายรังสีทั้งตัวร่วมกับเคมีบำบัดและการเปลี่ยนถ่ายไขกระดูกนี้ สามารถใช้ได้อย่างมีประสิทธิภาพสำหรับผู้ป่วยมะเร็งเม็ดเลือดขาวในเด็ก