Clinical Outcomes of Allogeneic Stem Cell Transplantation using Simplified Total Body Irradiation plus Chemotherapy in Adult Acute Leukemia; King Chulalongkorn Memorial Hospital experience.

ผลการรักษาของการฉายรังสีทั่วทั้งลำตัวแบบทำให้ง่ายร่วมกับการให้เคมีบำบัดก่อนการปลูกถ่ายไขกระดูกในผู้ป่วยผู้ใหญ่โรคมะเร็งเม็ดเลือดขาวระยะเฉียบพลัน; ประสบการณ์ในโรงพยาบาลจุฬาลงกรณ์

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Abstract

Background: Total body irradiation (TBI) is the important part of conditioning regimen before stem cell transplant in acute leukemia. Recently, we simplified TBI technique in our center. So, we conducted study to assess clinical outcome of TBI plus chemotherapy in adult acute leukemia.

Objective: The primary outcome was a 3-year overall survival (OS) and the secondary outcomes were engraftment rate, relapsed rate, acute graft-versus-host disease (GVHD), chronic GVHD, and late radiation toxicity.

Material and methods: We retrieved the retrospective data of post-TBI patients in adult acute leukemia between June 2014 and June 2016.

Results: Total enrollment was 12 adult acute leukemia patients (4 patients with new acute lymphoblastic leukemia (ALL), 4 patients with new acute myeloid leukemia (AML), and 4 patients with relapsed AML) with a median follow-up 3 years. Three-year OS was 74% (100% in new ALL, 100% in new AML, and 25% in relapsed AML). White blood cell (WBC) engraftment was 100%. Early relapsed rate within first year of transplantation was 25%, while late relapsed rate after first year of transplantation was 16.7%. Acute GVHD was 16.7% and finally turned to chronic GVHD. Chronic GVHD was affected 50% of all patients and 66.7% of surviving patients. There was neither toxicity grade ≥3of radiation pneumonitis nor a record of late radiation toxicity.

Conclusion: This TBI technique produced good transplantation outcomes in new adult acute leukemia group, accompanied by good tolerance. However, there were poorer outcomes in recurrent adult acute myeloid leukemia setting.

Keywords: Acute leukemia, Engraftment, Stem cell transplantation, Total body irradiation

บทคัดย่อ

หลักการและเหตุผล: การฉายรังสีทั่วทั้งลำตัวมีความสำคัญในการเตรียมปลูกถ่ายไขกระดูกร่วมกับการให้ยาเคมีบำบัดในโรคมะเร็งเม็ดเลือดขาวระยะเฉียบพลัน ช่วงที่ผ่านมาโรงพยาบาลจุฬาลงกรณ์ปรับเทคนิคการฉายรังสีให้สะดวกยิ่งขึ้น จึงเก็บการรวบรวมข้อมูลผลการรักษา

วัตถุประสงค์: เพื่อศึกษาผลการรักษาในแง่อัตราการรอดชีวิตที่ระยะเวลา 3 ปี, อัตราความสำเร็จในการปลูกถ่ายไขกระดูก, อัตราการกลับเป็นซ้ำของโรค, อัตราการเกิดภาวะสเต็มเซลล์ใหม่ต่อต้านร่างกายทั้งระยะเฉียบพลันและระยะเรื้อรัง รวมถึงผลข้างเคียงระยะยาวจากการฉายรังสี

วัสดุและวิธีการ: ทีมวิจัยเก็บรวบรวมข้อมูลการรักษาย้อนหลังของกลุ่มผู้ป่วยผู้ใหญ่โรคมะเร็งเม็ดเลือดขาวระยะเฉียบพลันที่ได้รับการฉายรังสีทั่วทั้งลำตัวระหว่างเดือนมิถุนายน 2557 ถึงเดือนมิถุนายน 2559

ผลการศึกษา: มีผู้ป่วยทั้งสิ้นจำนวน 12 รายภายในช่วงเวลาติดตาม3 ปีพบว่าอัตราการรอดชีวิตที่ระยะเวลา 3 ปีประมาณ 74% (ประกอบด้วยผู้ป่วยใหม่โรคมะเร็งเม็ดเลือดขาวระยะเฉียบพลัน ชนิดลิมฟอยด์ 100%, ชนิดมัยอิลอยด์ 100% และชนิดมัยอิลอยด์ที่กลับเป็นซ้ำ 25%) ผู้ป่วยทุกรายปลูกถ่ายไขกระดูกสำเร็จอัตราการเกิดภาวะสเต็มเซลล์ใหม่ต่อต้านร่างกายคิดเป็น 16.7% ในระยะเฉียบพลันและ 50% ในระยะเรื้อรัง (โดยผู้ที่มีภาวะสเต็มเซลล์ใหม่ต่อต้านร่างกายในระยะเฉียบพลันทุกรายจะเป็นต่อเนื่องไปถึงระยะเรื้อรัง)นอกจากนี้ยังไม่พบผลข้างเคียงระยะยาวจากการฉายรังสีในระดับที่จำเป็นต้องได้รับการรักษา

ข้อสรุป: การใช้เทคนิคการฉายรังสีทั่วทั้งลำตัวนี้ร่วมกับการให้ยาเคมีบำบัดช่วยให้การปลูกถ่ายไขกระดูกประสบความสำเร็จเป็นอย่างดีโดยเฉพาะกลุ่มผู้ป่วยใหม่โรคมะเร็งเม็ดเลือดขาวระยะเฉียบพลัน ในขณะที่ผลการรักษาในผู้ป่วยโรคมะเร็งเม็ดเลือดขาวระยะกลับเป็นซ้ำชนิดมัยอิลอยด์มีอัตรารอดชีวิตที่ต่ำกว่า

คำสำคัญ: มะเร็งเม็ดเลือดขาวระยะเฉียบพลัน, อัตราความสำเร็จในการปลูกถ่ายไขกระดูก, การปลูกถ่ายไขกระดูก, การฉายรังสีทั่วทั้งลำตัว

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Introduction

Acute leukemia consists of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Overall survival of ALL is better than AML, in both children and adult.[1] Acute leukemia in childhood has 10-year overall survival rate (OS) more than 80% when using primary chemotherapy and CNS prophylaxis by radiation or chemotherapy.[2] While acute leukemia in adolescent and adult, which has poor prognostic factors, has 5-year OS 17.7-63% by using chemotherapy alone.[3]

Conditioning regimen before ASCT is composed of chemotherapy with or without total body irradiation (TBI). From meta-analysis, chemotherapy plus TBI has better results than chemotherapy alone in both ALL ($p<.001$) and AML ($p=.04$).[4] Advantages of TBI include no sanctuary sites in the CNS and testis, independent of blood supply, no metabolism, and no excretion.

The main problem of TBI is that large target volume of 40x40 cm radiation fields cannot cover entire volume. Extended source-skin distance (SSD) technique and multiple small field technique were used to solve this problem. The first technique, 5-meter extended SSD can cover the target volume by 200x200 cm field size. There are various patient positions such as supine position, standing position, sitting position, or lateral decubitus position. The drawbacks of this technique are long treatment time due to 5-meter SSD, inhomogeneity, and the difficulty of placing lung blocks. The second technique, multiple small fields with supine and prone positions, overcomes the previous disadvantages of the extended SSD technique, however field overlapping of multiple small fields is the challenging point.

This retrospective descriptive study aims to analyzed only clinical data of current TBI procedure without comparison with the data of previous TBI procedure because of data missing. However, dosimetry was passed QA by physicists and was not shown in this study.

Material and Methods

Patients in KCMH with acute leukemia who received TBI before ASCT from June 2014 to June 2016 were included. Before 2014, TBI in King Chulalongkorn Memorial Hospital (KCMH) consisted of problematic complex tasks and redundant resource consuming. Therefore, our institution simplified procedure of TBI since June 2014. Current TBI procedures consisted of both 5-meter extended source to surface distance (SSD) and multiple small field techniques. Five-meter extended SSD technique covered the whole body of the patients in comfortable supine position by parallel-opposing lateral fields which based on 2 dimension technique. Two Gy per fraction (F) was delivered with high dose rate in the morning and evening for 3 days. Total dose was 12 Gy at head, legs and feet. The calculated dose of the thicker parts of the body, from shoulder to knee, was about 9 Gy. Therefore, additional boost about 3 Gy in a single fraction the next morning was delivered to the thicker parts of body by multiple small field technique using 4 isocenters, which based on 3D technique (CT on

the same day) and were changed by moving the couch instead of patients to produce accurate matching of beam divergence as shown in figure1. The radiation fields covering the body in anteroposterior and posteroanterior directions were divided into half beam with 90 degree collimator rotation in order to block the lungs by MLC.

Lung blocks using multileaf collimators (MLC) without the chest wall boost were applied to limit lung dose of 9 Gy. Patients were immobilized by thermoplastic material. Instead of a movable bed that placing on the floor, the linac couch was utilized, therefore, Electronic Portal Imaging device (EPID) and MLC were available instead of portable film and cerrobend blockage as shown in figure 2. Organ contouring was done for the lungs and kidneys which were blocked by MLC. Total treatment time was about 20 minutes per fraction. This technique was applied in KCMH without existing model from other institute.

The conditioning regimens of treatment in this study were started with the different induction and maintenance chemotherapy regimens by hemato-oncologist in our hospital then performed a TBI regimen in 4 consecutive days followed by Cyclophosphamide in 2 consecutive days and operated the ASCT.

Pediatric patients were excluded because of differences in treatment and prognostic factors. Clinical data were collected from electronic medical record. This study was approved by the ethics committee of KCMH.

Data consisted of age at TBI time, sex, disease, induction chemotherapy regimen, conditioning regimen before ASCT, acute graft-versus-host disease (GVHD) prophylaxis regimen, first TBI date, ASCT date, white blood cell (WBC) engraftment date, early-relapse date within 1 year, late-relapse date after 1 year, location of relapse, death date, last follow-up date, acute GVHD within 100 days, chronic GVHD at the last follow-up date, late radiation side effect at the last follow-up date and vital status at the data-collection date.

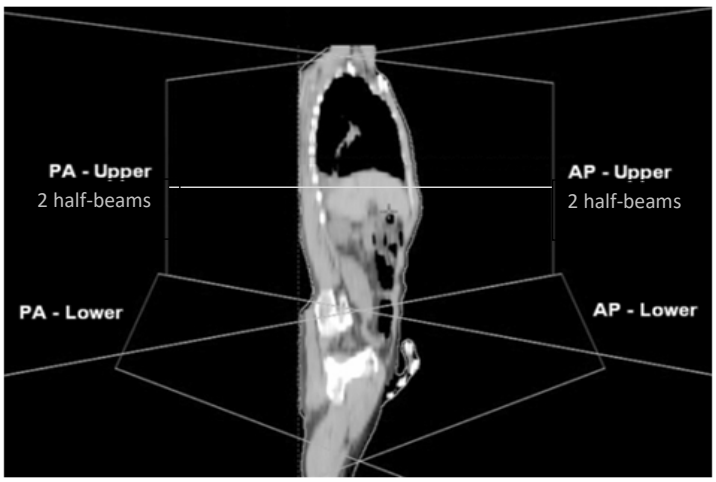

Figure 1: Accurate matching of 4 beams for additional boost to the thicker area

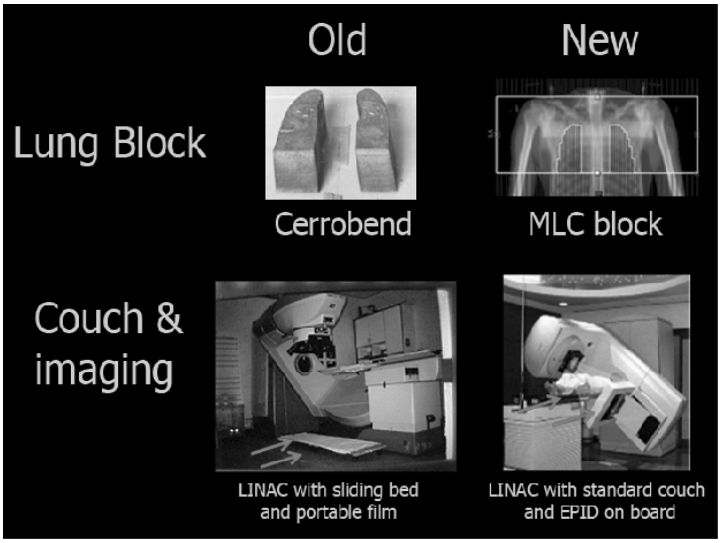

Figure 2: Comparison of modified devices including lung block, couch, and setup imaging

The primary endpoint was 3-year OS analyzed by Kaplan-Meier survival analysis. The survival time was calculated from the ASCT date to death date or vital status at the data-collection date. Secondary endpoints were WBC engraftment rate, the early relapse rate, the late relapse rate, the acute GVHD rate within 100 days, the late GVHD rate at the last follow-up date and late radiation side effect rate at the last follow-up date. The WBC engraftment was neutrophils ≥0.5x109/L after transplantation and the platelet engraftment was absolute Platelet count ≥ 20x109/L[5]. The early relapse rate was counted in the patient with recurrent disease within the first year of transplantation date. The late relapse rate was counted in the patient with recurrent disease after the first year of transplantation date. The acute GVHD was a clinical diagnosis with affecting of skin, bowel or liver, which was graded in table 1 supplement. The late GVHD was definitive pathological diagnosis with a variety of organ involvement. The late GVHD had clinical criteria with signs and symptoms shown in table 2 and 3 supplement. All secondary endpoints were analyzed in percentage.

Results

Twenty patients with acute leukemia who received TBI before ASCT from June 2014 to June 2016 were included. Eight pediatric patients were excluded. Patient characteristics are shown in table 1. Median follow-up time was 2.96 years (range 0.18-3.78 years). Mean age was 42.67 years (range 26-53 years). There were 9 male and 3 female. There were 4 ALL, 4 AML, and 4 relapsed AML. Induction chemotherapy regimens were hyper CVAD (consisted of Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone) in ALL, Cytarabine plus Daunorubicin in AML, and various regimens in relapsed AML. All patients received 12-Gy TBI plus Cyclophosphamide before ASCT and Methotrexate

Table 1: Patient characteristics

	Number	Percentage
Age	42.67 years (26-53 years)	
- mean (range)		
Sex		
- Male	9	75%
- Female	3	25%
Disease		
- ALL	4	33%
- AML	4	33%
- Relapsed AML	4	33%
Induction chemotherapy regimen		
- ALL - Hyper CVAD	4	33%
- AML - Cytarabine + Daunorubicin (7+3)	4	33%
- Relapsed AML		
• Cytarabine + Daunorubicin (7+3) + FLAG	1	8%
• Cytarabine + Idarubicin (5+2) + FLAG	1	8%
• FLAG	1	8%
• Cytarabine + Daunorubicin (7+3)	1	8%
Conditioning regimen before SCT		
- TBI 12 Gy + Cyclophosphamide	12	100%
Acute GVHD prophylaxis regimen		
- MTX + Cyclosporin	12	100%

Abbreviations: ALL = Acute lymphoblastic leukemia; AML = Acute myeloid leukemia; Hyper CVAD = Cyclophosphamide + Vincristine + Doxorubicin + Dexamethasone; FLAG = Fludarabine, high-dose cytarabine and G-CSF; TBI = Total body irradiation; GVHD = Graft-versus-host disease; MTX = Methotrexate

plus Cyclosporin for GVHD prophylaxis. Three-year OS was 74.04% as shown in figure 3. Subgroup analysis showed 3-year OS 100%, 100%, and 25% in ALL, AML, and relapsed AML, respectively.

Secondary endpoints are shown in table 2. WBC engraftment rate was 100%. Early-relapse rate within 1 year was 25%. Two relapse AML patients had recurrence in the blood and subsequently died at 2.1 and 7.8 months after ASCT date. Another high risk ALL patient had a recurrence in the meninges at 3.7 months but complete remission after salvage chemotherapy with follow-up time of 19.8 months (1.6 years). Late-relapse rate after 1 year was 16.7%. A relapse AML patient had recurrence in bone marrow and died at 26.4 months (2.2 years) after ASCT date. Another relapse AML patient had recurrence in skin at 13.2 months (1.1 years) but had complete remission after salvage chemotherapy with follow-up time of 46.0 months (3.8 years).

Acute GVHD rate within 100 days was found in 2 patients (16.67%), involving skin in the first patient and muscle in the other patient. Acute GVHD was treated and not resulted in death. All patients with previous acute GVHD turned to chronic GVHD. Chronic GVHD at last

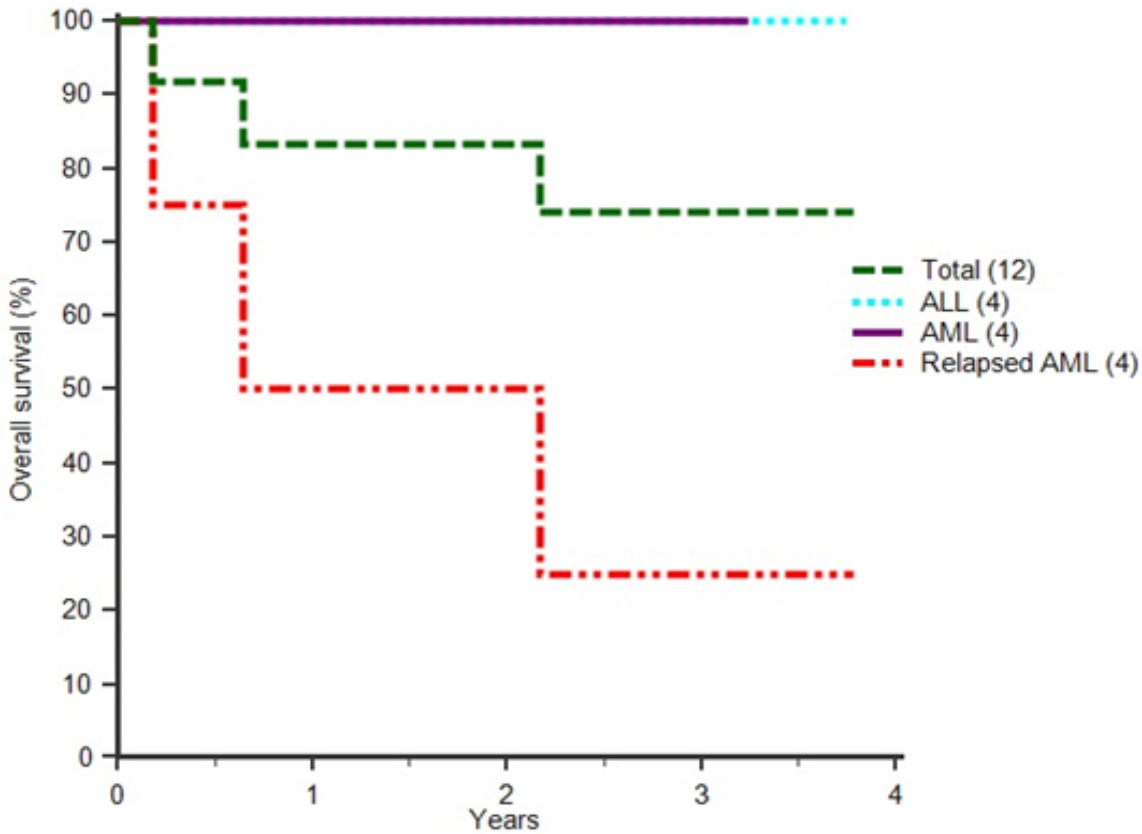

Figure 3: Overall survival (total and subgroup)

Table 2: Secondary endpoints

	Amount	Percentage
Engraftment rate	12	100%
- WBC engraftment	12	
- Platelet engraftment	12	
Early relapsed within first year	3	25%
- Blood (relapsed AML with death)	2	
- Meninges (ALL)	1	
Late relapsed after first year	2	16.7%
- Bone marrow (relapsed AML with death)	1	
- Skin (relapsed AML)	1	
Acute GVHD within 100 days	2	16.7%
- Skin	1	
- Muscle	1	
Late GVHD at last follow up date (at least 1 organ involvement)		
- TBI 12 Gy + Cyclophosphamide	6	50%
- Mouth	4	
- Eye	3	
- Liver	2	
- Skin	1	
- Lung	1	
- Muscle	1	

Abbreviations: WBC = White blood cell; ALL = Acute lymphoblastic leukemia; AML = Acute myeloid leukemia; GVHD = Graft-versus-host disease

follow-up date was found in 6 patients (50% of all patients, 66.67% of the surviving patients), involving multiple organs such as mouth in 4 patients, eye in 3 patients, liver in 2 patients, skin in 1 patient, lung in 1 patient, and muscle in 1 patient). Late radiation side effect rate at last follow-up date was 0%.

Discussion

TBI with 10-Gy single fraction was previously used in many institutions. It was necessary to prescribe a low dose rate to reduce radiation complication such as pneumonitis. Total treatment time was about 3.3-16.7 hours due to the dose rate of 1-5 cGy/min[6]. In contrast, low dose rate was not compulsory in fractionated TBI. Nowadays, TBI schedule is changed to be fractionation in order to reduce treatment time and radiation complication. A survey from 56 centers in 23 European countries showed that TBI schedules ranged from 8 Gy/1F to 14.4 Gy/8F (mostly 12 Gy/6F) and dose rates were 2.25-37.5cGy/min (mostly 16 cGy/min)[7]. The newer survey from 12 centers in Canada showed that TBI schedules were mostly 12 Gy/6F and dose rates were 9-51 cGy/min (mostly 14cGy/min)[8]. Therefore, TBI schedule of 12 Gy/6F and dose rate of 15 cGy/min in this study was reasonable and reducing treatment time to about 15 min/F.

Five-meter extended SSD technique produced 200x200 cm field size that absolutely covered patients in comfortable supine position and helped technicians to do faster and easier setup position. Total dose was 12 Gy at head, legs and feet while the calculated dose of the thicker parts of body including lung was about 9 Gy. Therefore, additional 3 Gy in a single fraction of the next morning was delivered to the thicker parts of body by multiple small field technique using 4 isocenters. A survey from 56 centers in 23 countries showed that lung blocks were used in 84% of centers and no chest wall compensation was done in 79% of the centers. Lung doses were 6-14.4 Gy (mostly 8 Gy)[7]. A survey from 12 centers in Canada showed that lung block was used in 83% of centers. Lung doses were 6-12Gy (mostly 8 Gy)[8]. Therefore, this study prescribed lung blocks without electron boost to the chest wall to limit the lung dose to about 8 Gy and reduce treatment complexity. Isocenters were changed by moving the couch instead of patients to produce accurate matching of beam divergence. Patients were immobilized by thermoplastic material. Instead of movable bed that placing on the floor, the linac couch was used, so Electronic Portal Imaging device and MLC were available to reduce technicians' workload. Our results suggested that this TBI schedule was achievable and tolerable, even there were various systemic chemotherapy due to variety of diagnosis.

Nowadays, the updated TBI guideline from the international lymphoma radiation oncology group (ILROG) consensus was published in April 2018[9], which supported TBI as an important part of conditioning regimen with patients of acute leukemia before hematologic stem cell transplantation. The details of TBI technique of our protocol were a bit of difference

from ILROG consensus, which treated patients with an extended SSD technique in standing or sitting positions, patient-specific compensating filter from head to feet, and critical organ blockage. Most centers shielded lung to keep the mean lung dose 8-10 Gy for prevention of radiation pneumonitis.

Three-year OS was 74% with 3-year median follow-up time. Four cases of ALL and 4 cases of AML showed 100% OS rate while 4 cases of relapse AML showed 25% OS rate. Report from Dana-Farber Cancer Institute and Harvard Medical School in 2002[10] with 200 patients showed engraftment rate 99.5%, 2-year OS 58% and relapse rate 24% after ASCT with TBI 14 Gy. But this report was proceeded in 1990-1998, which radiation technique and conditioning regimens before ASCT were not contemporary. Moreover, there was multiple diagnosis inclusion, such as AML, ALL, chronic myelogenous leukemia, second remission of ALL and AML, non-Hodgkin's lymphoma, and multiple myeloma, so the results could not be compared to our study. Report from Italy in 2016[11] with 211 patients of ALL showed 5-year OS 67.6% after ASCT with TBI 12 Gy. But this report consisted of most children (77.2%), which had better prognosis and differed from the population in our study.

Purposes of TBI are to suppress host's immunity and to eradicate the residual tumor cells. The WBC engraftment rate was 100%, while early-relapse rate within 1 year was 25%. Induction chemotherapy regimen and chemotherapy plus a TBI conditioning regimen before ASCT might not effective enough to eradicate tumor cells in some aggressive and uncontrollable cases because 2 of 3 patients with early relapsed disease within the first year were relapsed AML patients who had a recurrence in blood at 2.1 and 7.8 months after ASCT and finally died. While another early relapsed patient was initial ALL diagnosis who had a recurrence in meninges at 3.7 months after ASCT but complete remission after salvage chemotherapy with follow-up time of 19.8 months (1.6 years) after ASCT.

Acute leukemia is rapidly progressive disease, so late relapse after the first year may be due to minimal residual disease or new stimulus. Late-relapse rate after the first year was 16.7% from 2 relapsed AML patients. A patient with recurrence in bone marrow died at 26.4 months (2.2 years) after ASCT but another patient with recurrence in skin survived at the last follow-up time of 46.0 months (3.8 years) after ASCT.

In our cohort, acute GVHD was found in two patients (16.7%) which was less than the report of Jacobsohn et al, that acute GVHD rate was about 35-50%[12]. Two patients with acute GVHD were not dead and the disease turned to chronic GVHD. Chronic GVHD affected 6 patients of total 12 patients (50%), and 6 patients of 9 surviving patients (66.7%). From the report of Lee et al, incidence of chronic GVHD was in the similar range about 60-70%[13]. Chronic GVHD is one of the most common problems affecting long-term survivors of ASCT. The comprehension about chronic GVHD is insufficient to develop

early diagnosis or treatment. Delayed onset and dissimilarity of organ involvement conduct the complexity of investigating study, therefore incidence of chronic GVHD remains plenty.

There was no grade 3 or higher toxicity of radiation pneumonitis by CTCAE 4.0[14], which affected from mean lung dose restriction. No late radiation toxicity was observed in our cohort but this was retrospective manner with the relatively short period of follow-up time to conclude about late radiation toxicity.

Therefore, this simplified myeloablative regimen in our institution was effective and well tolerable. Although there was no record data of treatment time, this TBI technique was simpler than old technique and suspected less time consumer.

This study has limitation since it a retrospective descriptive study with small number of patients due to accessibility to ASCT in Thailand. We found a few comparative studies without gold standard data, so the analytic method was confined to percentage. The clinical data of previous TBI schedule from our institution was not well recorded enough to compare with the data from this study.

Challenge of clinical result conclusion was due to overlapping therapeutic effect of chemotherapy and radiation. There is no effective investigation to evaluate neither residual tumor cell nor normal host immune cell. Poor contemporary knowledge about chronic GVHD from disease complexity confines management and prophylaxis. The short follow-up time might cause absence of late adverse effect. Longer follow-up time with more population and stratified specific systemic treatment may provide the knowledge and the new standard of treatment. Additional new systemic treatment to myelosuppressive regimen, like immunotherapy or targeted therapy, is interesting and may assist therapeutic effect of the relapsed group.

Conclusion

This simplified TBI technique produced good transplantation outcome in adult with acute leukemia and had good tolerance. However, there was the poorer outcome in recurrent adult acute myeloid leukemia patients.

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Table 1 Supplement:

Stage of Acute GVHD by the number and extent of organ involvement.[12]

Extent of organ involvement			
Stage	**Skin**	**Liver (bilirubin)**	**Gut (stool output/day)**
0	No GVHD rash	< 2 mg/dl	< 500 ml/day or persistent nausea.
I	Maculopapular rash< 25% BSA	2–3 mg/dl	500–999 ml/day
2	Maculopapular rash 25 – 50% BSA	3.1–6 mg/dl	1000–1500 ml/day
3	Maculopapular rash > 50% BSA	6.1–15 mg/dl	Adult: >1500 ml/day
4	Generalized erythroderma plus bullous formation	>15 mg/dl	Severe abdominal pain with or without ileus
Grade			
I	Stage 1–2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	-	Stage 2–3 or	Stage 2–4
IV	Stage 4 or	Stage 4	-

Table 2 Supplement:

Clinical criteria for limited and extensive chronic GVHD.[13]

Original Seattle Classification	Revised Seattle Classification*
Limited	**Clinical limited**
One or both of:	1. Oral abnormalities consistent with chronic GVHD, a positive skin or lip biopsy, and no other manifestations of chronic GVHD
Localized skin involvement	2. Mild liver test abnormalities (alkaline phosphatase ≤2 × upper limit of normal, AST or ALT ≤3 × upper limit of normal, and total bilirubin ≤1.6) with positive skin or lip biopsy, and no other manifestations of chronic GVHD
Hepatic dysfunction due to chronic GVHD	3. Less than 6 papulosquamous plaques, macular-papular or lichenoid rash involving <20% of BSA, dyspigmentation involving <20% BSA, or erythema involving <50% BSA, positive skin biopsy, and no other manifestations of chronic GVHD
	4. Ocular sicca (Schirmer's test ≤5 mm with no more than minimal ocular symptoms), positive skin or lip biopsy, and no other manifestations of chronic GVHD
	5. Vaginal or vulvar abnormalities with positive biopsy, and no other manifestations of chronic GVHD
Extensive	**Clinical extensive**
One of:	1. Involvement of 2 or more organs with symptoms or signs of chronic GVHD, with biopsy documentation of chronic GVHD in any organ
Generalized skin involvement	2. Karnofsky or Lansky Clinical Performance scores <60%, ≥15% weight loss, and recurrent infections not due to other causes, with biopsy documentation of chronic GVHD in any organ
Localized skin involvement and/or hepatic dysfunction due to chronic GVHD, plus:	3. Skin involvement more extensive than defined for clinical limited chronic GVHD, confirmed by biopsy
Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, or:	4. Scleroderma or morphea
	5. Onycholysis or onychodystrophy thought to represent chronic GVHD, with documentation of chronic GVHD in any organ
Involvement of eye (Schirmer's test with <5 mm wetting), or:	6. Decreased range of motion in wrist or ankle extension due to fasciitis caused by chronic GVHD
	7. Contractures thought to represent chronic GVHD
Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, or:	8. Bronchiolitis obliterans not due to other causes
	9. Positive liver biopsy; or abnormal liver function tests not due to other causes with alkaline phosphatase >2 × upper limit of normal, AST or ALT >3 × upper limit of normal, or total bilirubin >1.6, and documentation of chronic GVHD in any organ
Involvement of any other target organ	10. Positive upper or lower GI biopsy
	11. Fasciitis or serositis thought to represent chronic GVHD and not due to other causes

Table 3 Supplement:

Signs, symptoms & clinicopathologic findings of chronic GVHD.[13]

System	Signs/Laboratory Findings	Symptoms	Histopathology
Skin (common)	Hyper- and hypopigmentation, lichen planus (violaceous flat-topped papules), poikiloderma (atrophy, telangectasias, dyspigmentation), cutaneous ulcers, scleroderma (thickening due to collagen deposition, may cause decreased range of motion and contractures), ichthyosis	Pruritis, lack of flexibility	Lichenoid: Hyperkeratosis, focal hypergranulosis, acanthosis, dyskeratotic keratinocytes, vacuolar degeneration, colloid bodies, perivascular and periadnexal lymphoplasmacellular infiltrate Poikiloderma: epidermal atrophy, loss of rete ridges Scleroderma: epidermal atrophy, dermal fibrosis, less inflammation than lichenoid lesion, adnexal structures destroyed Differential diagnosis: drug reaction, eczema
Cutaneous structures	Onchodystrophy, alopecia, loss of sweat glands	Heat sensitivity	Destruction and fibrosis of cutaneous appendages
Liver (common)	Elevated alkaline phosphatase, transaminases, bilirubin	Pruritis	Small bile duct atypia and damage with subsequent necrosis and drop-out, moderate lymphocytic infiltrate, cholestasis and ballooning Differential diagnosis: drug toxicity (cholestasis, inflammation), veno-occlusive disease, viral infections, gallstones, and infiltrative processes
Mouth (common)	Lichen planus, erythema, ulcers, xerostomia, dental caries, fibrosis, decreased salivary flow	Food sensitivity, pain, dry mouth, decreased oral range of motion from fibrosis	Mucosal atrophy, lymphoplasmacytic inflammation, increased mucopolysaccharides, fibrosis and destruction of minor salivary glands Differential diagnosis: Herpes virus infection, Sjogren's syndrome
Eyes (common)	Keratoconjunctivitis sicca, corneal ulcerations, Schirmer's test with <5 mm wetting at 5 min	Dry eyes, photophobia, pain	Differential diagnosis: postradiation xerophthalmia, Sjogren's syndrome
Esophagus	Esophageal web, desquamation, ulcerations, strictures, submucosal fibrosis, abnormal motility	Odynophagia, dysphagia, heartburn, retrosternal pain	Differential diagnosis: reflux esophagitis, infection
Intestines	Fibrosis, malabsorption	Diarrhea, nausea, anorexia, abdominal pain, weight loss	Differential diagnosis: irritable or inflammatory bowel syndrome, infection
Lung	Obstructive more than restrictive abnormalities on pulmonary function testing, BO, pneumothoraces, bronchiectasis, pseudomonal colonization, pulmonary infiltrates; air trapping on high resolution CAT scan of chest	Dyspnea, nonproductive cough, wheezing	BO with granulation tissue plugs and fibrosis obliterating small airways, interstitial pneumonitis
Musculoskeletal	Polymyositis, arthritis, fasciitis	Arthralgias, myalgias, weakness	
Serous	Pericardial, peritoneal, and pleural effusions	Clinical syndromes of cardiac tamponade, ascites, dyspnea	Usually transudative
Nervous	Entrapment of nerves, peripheral neuropathy, myasthenia gravis	Pain, paresthesias	
Urologic	Cystitis, phimosis	Pain, hematuria	
Vagina	Erythema, lichen-planus like, sicca, strictures, stenosis, ulcers	Pain, dyspareunia, difficulty voiding	
Hematopoietic	Thrombocytopenia, neutropenia, eosinophilia, hemolytic anemia		
Immune system	Lymphoid hypocellularity, hyper- or hypogammaglobulinemia	Frequent infections, especially sinus, upper respiratory tract	