

## Acute Response to Co-60 Total Body Irradiation (TBI) With 600 cGy at 3 Different Dose Rates in the Mice

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The acute effects of variable dose rates to total body irradiation (TBI) were investigated with 600 cGy of single exposure in the mice as a preclinical model. Total 80 mice (ICR) were used. Twenty of which served as controls, receiving no irradiation.

All irradiated mice showed a universal decline in their weight and white blood cell count. The degree of weight loss and leukopenia were similar at 3 different dose rates but slightly prominent with 15 cGy/minute group.

The degree of recovery among the groups showed no dose rate dependence. Our results suggest that TBI with 15 cGy/minute may be applicable for clinical therapy with careful evaluation of patient's condition.

**Key Words:** Total body irradiation; Dose rate; Acute effects

### INTRODUCTION

Bone marrow transplantation is a frequently employed treatment for certain types of hemopoietic and immune deficiency disorder<sup>1,2</sup>.

In order to achieve a successful graft, immunosuppression is required before transplantation. The most commonly used method of immunosuppression and tumor reduction is total body irradiation (TBI) with supralethal dose conjunction with high dose chemotherapy<sup>3</sup>.

TBI is usually administered at low-dose rate (5-10 cGy/min) in a large, single exposure<sup>4,5</sup>. There is a limit to the extent one can adjust the patient to the field size. In order to fit the field around patient, to enlarge the treatment distance, and to use the diagonal of the square field by collimator rotation are necessary.

The main disadvantage of the larger distance, however, may be the adverse effect on the treatment time.

Advantages of higher dose rates are that the machine time is decreased and that patient discomfort is shortened<sup>6</sup>.

Acute non-hemopoietic toxicity of TBI depended on the dose, the dose rate and the total treatment time and not on the fractionation regimen<sup>7</sup>.

The therapeutic effects may be increased by variations of dose, the dose rate and fractionation regimens as well as shielding of critical organs.

The optimal dose, dose rate and fractionation schedule has not been defined in our department,

therefore, we investigated the influence of dose rate on acute toxicity such as weight loss and peripheral blood changes which are important to evaluate patient's general condition to care one from post-TBI complication.

### MATERIALS AND METHODS

Eighty ICR mice of both sexes were used in the study (Table 1). All mice were  $30 \pm 1$  days old and body weights were  $25 \pm 2$  gm (male) and  $23 \pm 1$  gm (female), which were proper age group for animal experiments based on our previous report<sup>8</sup>.

The mice were irradiated with the same Co-60 teletherapy unit (C/9, ATC, 6000 Ci) used at the Yeungnam University Hospital through a build up layer of plastic approximately 0.5 cm thick.

For present study, three dose rates were chosen, 5, 10, and 15 cGy/minute, which fell within the range of dose rates in current clinical use for TBI with Co-60 teletherapy unit in our department.

The dose rates were measured using an 0.6 cc Farmer type ionization chamber, PTW 30-351 (PW-Freibury) and electrometer-500 (Victoreen).

All mice were evaluated for 9 weeks after TBI and analyzed changes of body weight, hemoglobin, WBC, and differential count.

### RESULTS

#### 1. Acute Effects on Body Weight

Progressive decline of body weight were seen from first to third, fourth, and the third week's follow

up, group I, II, and III respectively.

Recovery of weights were seen from sixth, fifth, and fifth week's follow up, group I, II, and III respectively.

There were no remarkable difference of weight loss or gain among the study groups.

## 2. Acute Effects on Hemoglobin

Slight decline of hemoglobin were seen in the first several week's follow up, afterthen nearly constant level of hemoglobin were seen, But there were no remarkable changes throughout the follow up period.

## 3. Acute Effects of White Blood Cell Counts

Nearly complete disappearance of WBC except

**Table 1. Study Grouping**

Groups	Total dose (cGy)	Dose rate (cGy / minute)	Number of mice (Male/Female)	
Control			10	10
Group I	600	5	10	10
Group II	600	10	10	10
Group III	600	15	10	10

several degenerated cells was seen from first to third week's follow up, from 4th week's follow up neutro-phils were major element of WBC but progressive decline of neutrophil counts and reciprocal increase of lymphocytes counts were seen. There were no dose rate dependence throughout the follow up period (Table 2).

## DISCUSSION

Allogenic bone marrow transplantation (BMT) has developed into a long effective therapy for the patients with hematologic malignancies, prior to bone marrow transplantation, conditioning therapies such as high dose chemotherapy and total body irradiation are necessary<sup>2-5</sup>.

Commonly available regimens include single agent or multiple agents combination chemotherapy in high dosage and total body irradiation using various techniques.

For recent several decades, a number of different approaches are described in which one can meet the technical requirements for TBI. The most important problems to solve are how to obtain a homogeneous dose distribution, and how to keep the dose below tolerance of critical organs<sup>10</sup>.

The different solutions to these problems have

**Table 2. Changes of Body Weight and Peripheral Blood Picture**

Follow up (weeks)		Pre RT	1	2	3	4	5	6	7	8	9
Body Weight (gm)	Control	23.5	24.1	25.4	26.1	25.5	29.4	30.7	31.5	29.3	30.8
	Group I	24.1	22.1	18.5	18.0	21.0	21.0	24.6	26.1	26.9	26.2
	Group II	23.6	21.5	19.7	18.3	18.1	24.0	26.0	26.0	26.4	27.5
	Group III	23.5	21.8	19.2	18.1	18.4	20.4	21.0	25.0	26.4	26.0
Hemoglobin (gm/100cc)	Control	15.0	14.9	15.0	14.8	14.7	15.0	14.8	15.0	13.2	14.1
	Group I	15.2	14.5	13.8	14.5	14.2	15.2	15.3	15.2	15.5	14.8
	Group II	15.3	14.7	13.4	14.3	15.8	15.8	14.3	14.3	14.9	15.0
	Group III	15.2	13.9	14.6	14.4	14.2	14.7	15.4	15.4	15.0	15.4
Lymphocyte counts	Control	67.0	61.3	64.5	65.6	66.7	69.5	64.3	63.5	64.0	68.3
	Group I	74.0	.	.	.	26.3	39.6	64.4	66.8	69.2	67.5
	Group II	73.7	.	.	.	16.0	47.0	54.0	71.0	72.0	70.0
	Group III	73.0	.	.	.	16.4	27.3	51.5	66.0	67.0	63.5
Neutrophil counts	Control	22.0	30.0	26.3	22.5	23.7	22.0	25.1	28.5	27.8	22.0
	Group I	13.6	.	.	.	61.8	47.6	25.6	22.8	18.0	20.3
	Group II	13.6	.	.	.	70.0	35.0	31.0	19.0	14.0	19.0
	Group III	16.0	.	.	.	72.8	50.0	39.0	19.0	20.5	25.0

Control group : No irradiation  
Group II : 10 cGy / minute

Group I : 5 cGy / minute  
Group III : 15 cGy / minute

their advantages and disadvantages. These are, however, two factors which seem to play an important role in the determination of the technique of choice.

The first is the treatment schedule; single dose or fractionation, high dose rate or low dose rate.

The treatment schedule is of direct influence on treatment time and on the number of treatment sessions<sup>6)</sup>. This in turn leads to the patient's comfort, the reproducibility of his position, and on the accuracy of the radiation.

The second is determined by local circumstances, such as the maximal obtainable field size and the available irradiation machine.

The original technique developed at Seattle used simultaneous radiation from 2 opposed Co-60 sources to treat anterior and posterior, then 2 lateral fields.

A total dose of 1000 cGy was administered as a single fraction using a low dose rate of 5 cGy/minute<sup>5,11,12)</sup>.

Most centers lack the purpose-built equipment to reproduce this technique and have had to modify it.

The university of Minnesota team used 2 lateral large fields on a 10 MeV linear accelerator. A total dose of 750 cGy was administered as a single fraction with a dose rate of 25 cGy/minute which was considered biologically equivalent to the Seattle technique<sup>9)</sup>.

In present study we choose 600 cGy single exposure corresponding to LD 50/30 of the mice<sup>13)</sup> with 3 different dose rates, 5, 10, and 15 cGy/minute which took 120, 60, and 40 minutes, respectively.

Radiation damage of the hematopoietic tissue upsets normal balance between the circulation blood cells, the rate of replacement, and the body's demand for them by reducing or interrupting the supplying of blood cells. The circulating lymphocyte is sufficiently sensitive to total body irradiation, unlike the other circulating formed elements.

Many reports<sup>14,15)</sup> suggested the most prominent acute effect of total body irradiation is a reduction of circulating lymphocyte count but hemoglobin value was more resistant than white blood cells. In present report, decline of body weight began from first week of follow up but after 6 th weeks of follow up showed recovery to pretreatment level and progressive weight gain was seen irrespective to dose rate. Hemoglobin level was nearly constant throughout the study, which suggests erythrocyte is highly resistant to 600 cGy,

TBI at 5-15 cGy/minute dose rate range.

In the case of white blood cell, the first week's examination showed almost all of the white cell were not seen and lasting up to 4th weeks follow up. From 5th week's examination, neutrophil count rose prominently with reversed lymphocyte/neutrophil ratio but no dose rate dependence.

Two to three weeks after this phenomenon lymphocyte count recovered to pretreatment level and kept their constant levels.

These findings were similar to the report of Lee et al<sup>6)</sup> in the case of whole abdominal irradiation in the mice.

## CONCLUSION

We have analyzed acute response to total body irradiation 600 cGy single exposure, with 3 different dose rates (5, 10, and 15 cGy/minute) in 80 ICR mice. Obtained results are follows:

1. All irradiated mice showed universal decline in their body weight and white blood cell count with no dose rate dependence.
2. The lymphocytes were most sensitive to TBI but showed complete recovery after 9 weeks of follow up with no dose rate dependence
3. The neutrophils were early appearing white blood cell from 4th weeks' follow up with no dose rate dependence.

Above mentioned analyses demonstrate that TBI with increased dose rate up to 15 cGy/minute could be performed in the mice with no demonstrable additional toxicity but further study using other various animals or treatment regimens should be carried out before clinical application.

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— 국문초록 —

**코발트-60 원격치료기를 이용한 전신 방사선 조사에서 선량율의 차이에 따른 급성효과**

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영남대학교 의과대학 치료방사선과학교실에서는 코발트-60원격치료기를 이용하여 80마리의 ICR 백서를 대상으로 서로다른 세가지 선량율로 600 cGy 단일조사를 시행한뒤 9주일동안 체중 및 말초혈액소견의 변화를 추적조사한 결과 다음과 같은 성적을 얻었다.

1. 체중변화는 선량율에 상관없이 조사 1주일부터 감소하여 6-7주일부터 치료전의 체중까지 회복되었다.

2. 혈액색소의 변화는 전 추적조사기간에 걸쳐서 변화가 없었다.

3. 말초 혈액내의 백혈구의 총수는 조사 1주일부터 3주일까지 형태학적 구분이 안되는 수개의 세포만이 인지되었고 4주일부터 호중구의 회복이 임파구에 비해서 현저하였으며 8-9주일부터 조사전의 상태로 완전 회복되었다.

이상의 결과를 토대로 보다 다양한 실험을 거친후 저선량율 전신조사의 가장 큰 단점인 장시간의 조사로 인한 기계의 무리와 환자 위치고정의 해결을 위하여 분당 선량율을 15 cGy까지 올릴 수 있으리라 기대된다.