Splenic Irradiation in Chronic Myelogenous Leukemia

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Radiation therapy was the treatment of choice for CML in the past, in the form of SI or radioactive phosphorus. Its use has been replaced to a large extent by various chemotherapeutic agents. Recently SI in CML has been used, both to relieve painful splenomegaly and to take advantage of an indirect effect of SI on unirradiated bone marrow.

We have treated 15 CML cases who had a huge spleen during chemotherapy or even after chemotherapy by 6 MV linear accelerator during the past two years at the Division of Radiation Therapy, Kang Nam St. Mary's Hospital, Catholic College.

Response to SI has been rated according to the scoring system of Roger W. Byhardt, et al. which evaluated the splenic and hematologic response as well as the response of disease-related systems. According to this scoring system, most patients demonstrated a significant relief of splenomegaly along with improvement of hemogram. And we observed the change of Karnofsky Performance Status after SI, and survival after a confirmative diagnosis and SI.

Key Words: Splenic irrdiation. Chronic myelogenous leukemia. Splenomegaly

INTRODUCTION

It has been known since 1903 that clinical and hematologic remissions in CML, a generalized disease, follow irradiation therapy localized to the spleen. SI had been widely used for CML before the chemotherapy with busulfan was introduced as preferred treatment. Recently SI has been used to relieve painful splenomegaly or for accelerated phase or retractable case to chemotherapy, even though the result of SI alone is worse than that of chemotherapy.

SI has direct and indirect effect such as regression of spleen, reduction of leukocyte count, and increase of hemoglobin level. It has also been apparent that the beneficial effects of irradiation persist for some time after the cessation of therapy, and SI may be repeated in case of satisfactory response to SI. Sometimes clinical improvement may be seen after SI in case of no response to chemotherapy and more desirable response may be expected in case of fewer treatment before SI.

We have treated the 15 CML cases who had huge spleen with or without pain during chemotherapy or even after chemotherapy by 6 MV linear accelerator at the Division of Radiation Therapy, Kang Nam St. Mary's Hospital during the past two years. We have observed the splenic and hematologic response as well as the response of disease-related symptoms and survival of patients.

MATERIALS AND METHODS

We have treated 15 CML patients who had huge spleen with or without pain during chemotherapy or even after chemotherapy at the Division of Radiation Therapy, Kang Nam St. Mary's Hospital, Catholic Medical College, from June 1983 through August 1985. SI was accomplished with a 6 MV linear accelerator utilizing a shaped field with the source axis distance (SAD) 80cm. The field size was determined according to the size of palpated spleen and splenic

contour as it appeared on the simulation film. A part of liver, stomach, intestine, and right kidney within the field were shielded with 5 HVL of Pb. Ten out of 15 cases were treated anterioly and the rest (Cases 5,6,8,14 & 15) were treated AP:PA with the ratio of 3:2. We estimated the size of spleen by palpation everyday to evaluate the response to SI and reduced the field size as splenomegaly regressed. Daily dose was 25-50 cGy in severe splenomegaly and 50-100 cGy in mild to moderate splenomegaly. The total dose ranged from 250 to 1000 cGy in 8 to 31 days as was determined by dose rate, clinical, physical, and hematologic response.

SI was done by the method shown in Table 1. Response to SI of each patient was scored for each response category by the semi-quantitative method of Roger W. Byhardt[1] as outlined in Table 2. We observed the change of splenic pain, splenomegaly, peripheral WBC and platelet counts, hemoglobin level, and lymphadenopathy after SI (Tables 3,4). And we observed the change in spleen size, and Karnofsky Performance Status and survival after a confirmative diagnosis and SI.

RESULTS

Fifteen cases consisted of 12 males and 3 females (male : female = 4 : 1). Age distribution was from 4 to 74 years of age. They were 7 cases in fifth decade, 4 cases in third decade, 2 cases after seventh decade, and each 1 case in second and first decade. Most cases were in fifth decade.

Twelve cases finished the total treatment planned and interrupted 3 cases consisted of 2 cases of severe leukopenia (Cases 2,6) and 1 case of progression to blast crisis (Case 9).

Response to SI was rated according to the scoring system of Roger W. Byhardt (Table 2) and the results were as follows (Tables 3,4,5).

Splenic pain was present in 2/15 cases (Cases 5,11) and partially relieved after SI in both cases.

Splenomegaly was reduced in 13/15 cases, not reduced in 2/15 cases, and not aggravated in any case. Splenomegaly was reduced 50% or more in 7/15 cases (Cases 4,8,12-15), 25-50% in 4/15 cases (Cases 2,3,6,11), and 25% or less in 2/15 cases (Cases 5,7).

The response of the peripheral hemogram is outlined by scoring system in Table 3 and by selected values of hemoglobin, WBC count, and platelet count in Table 4.

The peripheral WBC showed a 75% reduction or more and to below 10,000/mm³ in 8/15 cases (Cases 2,3,6,8,12-15), and at least 75% reduction

Table 1. SI Technique in 15 CML Patients with Splenomegaly

Case No.	Age/Sex	F.S. (cm)	Port	Daily dose cGy/day	Total dose/elapsed day cGy/days
1	23/M	16×20−12×16	AP	50−100	900/11
2*	48/F	18×17−12×15	AP	50	500/12
3	45/M	19×22−12×16	AP	50−25	425/13
4	47/M	8×16− 6×10	AP	50	250/ 8
5	41/M	16×18	AP:PA=3:2	45	225/ 8
6*	23/F	13×25	AP:PA=3:2	50	150/ 5
7	17/M	23×25−18×18	AP	20−50	200/11
8	44/M	15×25−14×21	AP:PA=3:2	50	200/ 4
9*	49/M	12×17	AP	50	450/18
10	4/M	6×14− 6× 7	AP	30−50	570/54
11	68/F	10×17	AP	50	300/ 9
12	27/M	11×20	AP	50	270/10
13	48/M	12×19−10×12	AP	50	400/12
14	29/M	12×20− 8×16	AP:PA=3:2	50	700/21
15	74/M	12×22− 9×18	AP	30	1000/31
			AP:PA=3:2	50	

F.S.: field size SI: splenic irradiation
CML: chronic myelogenous leukemia 12-13 mg/dl
* interrupted case during SI

but not to below 10,000/mm³ in 1/15 case (Case 7), and less than 75% reduction in 1/15 case (Case 5). The peripheral WBC was not reduced in 2/15 cases (Cases 10,11), and was below 10,000/mm³ before SI in 3/15 cases (Cases 1,4,9).

Platelet count was below 50,000/mm³ after SI even though they rose after SI in 2/15 cases (Cases 8,10). Another large portion of cases, 13/15, showed a stability and/or slight increase of counts already above 50,000/mm³.

Table 2. Scoring System for Judging Clinical and Hematologic Response to SI. (Roger W. Byhardt, M.D. 1975*)

A. Splenic pain (SP)
- X not present
- 1 completely relieved
- 2 partially relieved
- 3 not relieved

B. Splenomegaly (SM)
- 1 palpable extent below left costal margin (LCM) reduced to nonpalpable or measurement below LCM reduced 50%
- 2 palpable extent below LCM reduced 25-50%
- 3 palpable extent below LCM reduced 25% or less

C. peripheral WBC (WBC)
- X not elevated above 10,000/mm³
- 1 reduced to below 10,000/mm³, 75% reduction or more
- 2 reduced at least 75%, but not to below 10,000/mm³
- 3 reduced, but less than 75%
- 4 not reduced

D. Platelet count (PLT)
- 1 increase post-treatment and above 50,000/mm³
- 2 stable post-treatment above 50,000/mm³
- 3 stable post-treatment below 50,000/mm³
- 4 decrease post-treatment and below 50,000/mm³

E. Hemoglobin (HB)
- 1 unchanged, above 12-13mg/dl, or rose to this level
- 2 stable below 12-13 mg/dl, or increased, but not to 12-13 mg/dl,
- 3 fell below 12-13 mg/dl, or fell while already below 12-13 mg/dl

F. Lymphadenopathy (LA)
- X none present
- 1 reduced 50% or more
- 2 reduced, but less than 50%
- 3 not reduced

* (Cancer 35: 1621-1625, 1975)
from Roger W. Byhardt et al. in Reference 1

Hemoglobin remained unchanged in 2/15 cases (Cases 6,15) already above 12-13 mg/100ml or rose to this level, while 6/15 (Cases 3,5,11-14) were stable below 12-13 mg/100ml or increased but not to 12-13 mg/100ml, and in 7/15 (Cases 1,2,4,7-10,15) slightly decreased just after SI.

Lymphadenopathy was present in 2 cases (Case 3 in both inguinal areas and Case 4 in both neck and inguinal areas) and was not changed just after SI in both cases.

Survival after SI could be evaluated in 13/15 cases. 7/15 cases were dead and had survived with a range of 1 week to 14 months after SI, and 6/15 cases are alive and have survived with a range of 2 weeks to 15 months after SI.

Karnofsky Performances Status was improved after SI in 8/15 cases.

CASE (Case 14)

A salariat, 29-year-old man was admitted to the hospital due to the large LUQ mass palpated incidentally by himself and severe fatigability. He had visited the local clinic and abnormal finding had been seen in hematologic examination.

There was a past history of hepatitis, 10 years ago.

On physical examination the huge splenomegaly (spleen size;* $a \times b = 19 \times 18$cm;* See Table 5) was seen, and hepatomegaly or lymphadenopathy was not seen. Hemoglobin was 8.9 g/100ml; the

Table 3. Response to SI of each Patient in 15 CML Patients

Case No.	Age/Sex	SP	SM	WBC	PLT	HB	LA
1	23/M	X	1	X	2	3	X
2	48/F	X	2	1	2	3	X
3	45/M	X	2	1	1	2	3
4	47/M	X	1	X	1	3	3
5	41/M	2	3	3	2	2	X
6	23/F	X	2	1	2	1	X
7	17/M	X	3	2	1	3	X
8	44/M	X	1	1	3	3	X
9	49/M	X	3	X	1	3	X
10	4/M	X	3	4	3	3	X
11	68/F	2	2	4	1	2	X
12	27/M	X	1	1	2	2	X
13	48/M	X	1	1	2	2	X
14	29/M	X	1	1	2	2	X
15	74/M	X	1	1	1	1	X

white cell count was 185,000/mm³ with 29% segmented neutrophils, 26% stab neutrophils, 3% lymphocyte, 1% monocyte, 5% eosinophils, 4% basophils, 32% immature forms; the hematocrit was 27%; the platelet count was 518,000/mm³. The urine gave a + test for protein; negative test for sugar; the sediment contained 5-7 red cells and 0-1 white cell per high-power field. The liver enzymes were normal.

On the second hospital day the bone marrow aspiration biopsy was performed and he was confirmed as CML.

On the third as fourth hospital day, Vp 16 160 mg was injected intravenously, and from the fourth

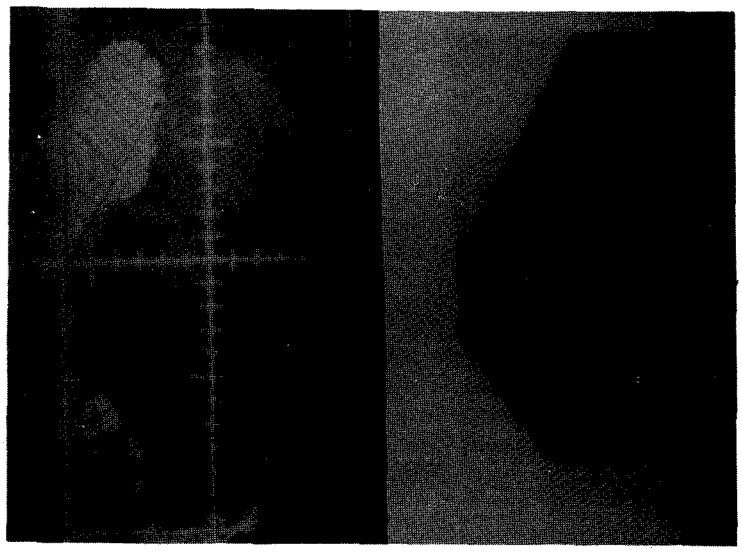


Fig. 1. Simulation Film and Linacgram at the Beginning of SI in Case 14.

Table 4. Hematologic Changes before and after SI in 15 CML patients

Case No.	Age/Sex	HB (mg/dl) pre-/post-SI	WBC (1,000/mm³) pre-/post-SI	PLT (1,000/mm³) pre-/post-SI
1	23/M	11.1/10.8	5.4/ 3.5	466/384
2	48/F	10.6/8.7	11.6/2.0	466/386
3	45/M	7.2/8.9	47.6/6.0	264/740
4	47/M	12.8/11.4	7.7/5.0	120/125
5	41/M	7.4/ 9.4	48.0/42.5	960/538
6	23/F	12.6/12.0	43.8/3.2	140/120
7	17/M	11.3/10.1	165.6/30.0	268/532
8	44/M	9.8/ 9.2	28.0/ 5.9	13/ 22
9	49/M	8.7/ 8.5	8.6/ 5.0	124/178
10	4/M	10.5/ 8.4	3.5/46.7	21/ 35
11	68/F	9.0/10.3	21.6/22.5	52/ 68
12	27/M	9.9/10.4	19.6/ 3.3	480/374
13	48/M	10.5/10.6	433.0/ 2.7	500/402
14	29/M	8.9/10.6	185.0/ 2.7	518/243
15	74/M	12.7/12.3	18.9/ 7.6	150/274

HB: hemoglobin WBC: leukocyte
PLT: platelet count

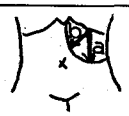
hospital day hydroxyurea 3 g was administered per oral daily. With response to chemotherapy leukocyte count was reduced. On the seventh hospital day hemoglobin was 10.3 g/100ml; the white cell count was 77000/mm³; the hematocrit was 32%; the platelet count was 468,000/mm³. Hydroxyurea was taperred from the seventh hospital day.

But the splenomegaly was not reduced during chemotherapy, so SI was started on the eighth hospital day. On physical examination huge splenomegaly was seen and the size of the spleen was 15(a) × 14(b) cm. SI was accomplished with a 6 MV linear accelerator utilizing a shaped field with the SAD 80cm, the field size 10×20cm, and the daily dose 50 cGy/d, treated AP:PA daily with the ratio of 3:2 (Fig. 1).

After 200 cGy/4d the spleen was regressed (spleen size; a×b = 9×9 cm) and leukocyte count was decreased (hemoglobin 11.2 g/100ml, hematocrit 35%, white cell count 45,500/mm³, platelet count 650,000/mm³). The spleen size was measured daily with reduction of field size according to the regression of spleen (Field size; from 12×20 cm to 8×16cm; Fig. 2).

Table 5. Changes in Spleen Size and Karnofsky Performance Status before and after SI, and Survival

Case No.	Age/Sex	Spleen size (cm) pre-SI a/b	Spleen size (cm) post-SI a/b	Survival post-SI (post-C.Dx)	KPS pre-SI..post-SI
1	23/M	17/12	5/ 5	10 m (6 y) DOD	50-60..60-70
2	48/F	19/18	10/11	14 m (12 y) DOD	50-60..60-70
3	45/M	20/18	11/10	6 m (10 m) DOD	50-60..50-60
4	47/M	11/ 8	5/ 4		50-60..60-70
5	41/M	10/10	8/ 8	1 w (16 m) DOD	50-60..50-60
6	23/F	19/15	15/10		50-60..50-60
7	17/M	15/17	13/14	15 m (22m) Alive	60-70..70-80
8	44/M	12/18	4/ 2	6 m (1 y) DOD	40-50..60-70
9	49/M	13/10	13/10	2 w (4 y) DOD	70-80..40-50
10	4/M	11/ 8	11/ 8	6 m (10 m) DOD	60-70..50-60
11	68/F	16/10	12/ 6	8 m (9 m) Alive	50-60..70-80
12	27/M	11/ 8	5/ 4	4 m (5 m) Alive	60-70..70-80
13	48/M	12/10	0/ 0	3 m (4 m) Alive	60-70..70-80
14	29/M	15/14	4/ 4	3 w (2 m) Alive	70-80..70-80
15	74/M	18/15	8/ 4	2 w (1 m) Alive	70-80..70-80



a: palpable extent of spleen below left costal margin in mid-clavicular line
b: the longest from top of 'a' to medial margin of palpable spleen
C.Dx: confirmative diagnosis DOD: dead of disease

After 700 cGy/21d the spleen size was 3(a)×3(b) cm and hemoglobin was 10.6 g/100ml; the white cell count was 2700/mm³; the platelet count was 243,000/mm³. So SI was finished.

DISCUSSION

CML is the acquired disease of disorder of hematopoietic stem cell proliferation, and characterized by marked expansion of granulocytes.[2,3] CML is easily diagnosed by splenomegaly, leukocytosis, increased absolute count of basophils and eosinophils, the presence of Philadelphia chromosome, and decreased activity of leukocyte alkaline phosphatase.[3-5] Treatment consists of chemotherapy, radiotherapy, splenectomy, leukapheresis, and BM transplantation. The mean survival is 36 months to 44 months.[3-5] Most of patients are stable until accelerated phase or blast crisis, if they are well treated. But Philadelphia chromosome negative CML patients characteristically do poorly with therapy and have a mean survival in the range of 14 months to 19 months.

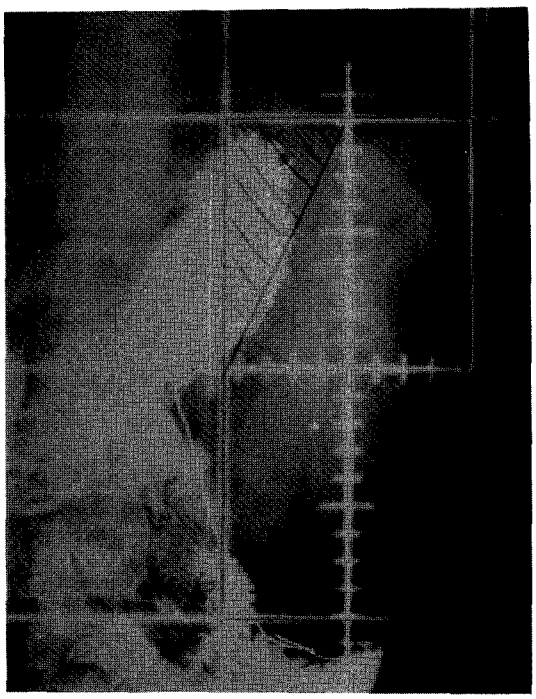


Fig. 2. Simulation film at total dose of 200 cGy (50 cGy/d, 5 fx/wk) in case 14.

For half a century before 1940s the radiation therapy (SI or radioactive phosphorus ^{32}P) had been the preferred treatment,[3,6,7] although recently chemotherapy has been known as preferred treatment of CML. In the 1940s the first of several new groups of cytotoxic drugs became available,[6,7] and some of these were found to be of value in the treatment of CML. Busulfan with its relative freedom from side effects and known efficacy and ease of handling in the treatment of CML, was thought by many physicians to be at least as effective as radiotherapy and perhaps more effective (1953, Haddow and Timmis[6]). It was well known that sometimes patients who did not respond to SI might respond to busulfan. It has also been suggested from observation on a small uncontrolled series that patients who received radiotherapy and busulfan in sequence survived longer than those who were treated by either method alone (Wiltshaw and Galton, 1958).[6] But the two methods had never been compared on a random basis in a controlled clinical trial. Also the result of SI alone has not been reported due to rarity of its case, recently. Since some stress has been placed on the importance of initial therapy, Monfardini, et al.[7] analyzed the survival of patients initially treated with chemotherapy as compared with those treated first with radiation therapy. Using the group of 84 patients treated with both chemotherapy and radiation therapy, 42 had chemotherapy and 42 had SI as initial primary therapy. The patients treated initially with chemotherapy had a median survival of 28 months and mean of 34 months (range 4-80 months). Patients treated initially with SI had a median survival of 30 months and mean of 38 months (range 4-142 months). The differences were not significant statistically. Recent comparative studies have stressed the superiority of busulfan over SI. However, Gollerkeri and Shah[7,8] suggested that the socioeconomic status of their patients may have influenced the adequacy of therapy and follow-up care and therefore may have been a significant factor in the poorer response of SI compared to chemotherapy in their series. Many authors have reported about SI as the treatment of CML.

Now, chemotherapy is the preferred treatment in CML and SI is used as adjuvant therapy in cases of huge splenomegaly with or without pain during chemotherapy or even after chemotherapy.

SI has the direct and indirect effect such as regression of the spleen, reduction of leukocyte count, and increase of hemoglobin level. Parsons[9] and associates have studied the indirect effect in the

unirradiated bone marrow by taking serial marrow biopsies during SI of CML patients. SI produces massive death of leukemic cells in spleen and improved function of bone marrow, and the patients showed decreased count of leukocyte, increased level of hemoglobin, and improved status of BM examination (Hotchkiss and Block, 1961[9,10]). The spleen acts as a source of supply for a large proportion of leukemic cells and also acts as a trap for normal and abnormal leukocytes. We observed that the splenomegaly was reduced in 13/15 cases, and the peripheral WBC was reduced in 13/15 cases.

The main feature of CML group was a 1.3 to 2 times increase in the rate of red cell destruction with failure of the erythropoietic tissues to respond adequately to the developing anemia. The normal or slightly increased rate of hemoglobin synthesis over normal was in no case adequate to compensate for the decreased RBC survival. Qualitatively, extremedullary erythropoiesis was a constant feature with premature delivery of erythrocytes into the circulation as shown by the number of ciculating normoblasts. Splenic irradiation seemed to suppress the process leading to increased red cell sequestration so that the hemoglobin pool could be restored without and appreciable alteration in the rate of hemoglobin synthesis (Awwad 1966[9,11]). In addition following irradiation a shift of erythropoietic activity from extramedullary sites to the bone marrow occured. We observed that in 2/15 cases anemia was absent, in 6/15 cases hemoglobin level rose, but not to 12-13 mg/100ml, and in 7/15 cases hemoglobin level slightly decreased just after SI.

The dose range of our 15 cases was 250-1000 cGy in 8 to 31 days, and was determined by dose rate, clinical response, physical response, and hematologic response. And the daily dose was in the range from 25 to 100 cGy according to the size of the spleen. Most of patients were treated anteriorly and 5/15 cases were treated AP:PA with the ratio of 3:2.

CONCLUSION

We have treated 15 CML cases by SI who had huge spleen with or without pain during chemotherapy or even after chemotherapy by 6 MV linear accelerator at the Division of Radiation Therapy, Kang Nam St. Mary's Hospital, Catholic Medical College, from June 1983 to August 1985.

Response to SI has been rated according to a scoring system used by Roger W. Byhardt, et al. which evaluated the splenic and hematologic response, as well as the disease-related symptoms. Also we observed the change of Karnofsky Performance Status after SI and the survival after a confirmative diagnosis and SI.

1. 15 cases consisted of 12 males and 3 females (male : female = 4 : 1). Age distribution was from 4 to 74 years of age Most cases were in fifth decade.
2. Splenic pain was present in 2/15 cases and partially relieved after SI in both cases.
3. Splenomegaly was reduced in 13/15 cases, not reduced in 2/15 cases, and not aggrevated in any case. Splenomegaly was reduced 50% or more in 7/15 cases, 25-50% in 4/15 cases, and 25% or less in 2/15 cases.
4. The peripheral WBC showed a 75% reduction or more and to below 10,000/mm^3 in 8/15 cases, and at least 75% reduction but not to below 10,000/mm^3 in 1/15 case, and less than 75% reduction in 1/15 case. The peripheral WBC was not reduced in 2/15 cases, and was below 1,000/mm^3 before SI in 3/15 cases.
5. Platelet count was below 50,000/mm^3 after SI even though they rose after SI in 2/15 cases. Another large portion of cases, 13/15, showed stability and/or slight increase of counts already above 50,000/mm^3.
6. Hemoglobin was already above 12-13 mg/100 ml in 2/15 cases, increased but not to 12-13 mg/100ml in 6/15 cases, and slightly decrease just after SI in 7/15 cases.
7. Survival after SI could be evaluated in 13/15 cases. 7/15 cases were dead and had survived with a range of 1 week to 14 months after SI, and 6/15 cases are alive and have survived with a range of 1 week to 14 months after SI, and 6/15 cases are alive and have survived with a range of 2 weeks to 15 months after SI.
8. Karnofsky Performance Status was improved after SI in 8/15 cases.

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=국문초록=

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가톨릭의과대학 방사선치료실 및 내과학교실*

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전신질환인 만성골수성백혈병(Chronic Myelogenous Leukemia; CML)에 있어서, 비장에만 국소적으로 방사선을 조사(Splenic Irradiation; SI)함으로써, 임상적 증상의 호전과 혈액소견상에 완해를 일으킨다는 것은 1903년대 이후로 알려져 있는 사실이다. 최근에 와서 Busulfan에 의한 화학요법이 주치료로서 도입되기 전까지는 SI가 CML치료에 광범위하게 사용되어 왔었다. 요즈음엔 비장의 방사선치료는 화학요법보다 그 결과가 좋지 못하지만, 통증을 동반한 비종대에서 증상의 완화를 위하거나, 가속기(accelerated phase)에 들어섰거나, 화학요법에 반응하지 않을 때 사용되고 있다.

SI의 효과는 백혈구수의 감소, 헤모글로빈치의 상승등의 직접, 간접효과가 있으며 이 효과는 방사선치료를 끝낸후에도 어느기간 지속되며, 만족스런 반응을 보일 경우엔 반복치료도 시도되고 있다. 그리고 약물치료에 반응이 없었던 환자에서도 때로는 SI로 임상적 호전을 관찰할 수 있으며, SI전에 많은 치료를 받지 않았던 경우에 더 좋은 반응을 기대할 수 있음은 잘 알려져 있다.

가톨릭의대 방사선치료실에서는 화학요법도중 통증을 동반한 심한 비종대를 호소하거나, 화학요법에 반응이 없었던 15례의 CML환자에서 SI를 실시하였다. 저자들은 대상환자들의 SI전후의 임상적 증상, 이학적 소견 혈액학적 소견등의 변화 및 생존기간을 추적하였기에 문헌고찰과 함께 보고하는 바이다.

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