The Effect of Intermittent Craniospinal Irradiation and Intrathecal Chemotherapy for Overt Meningeal Leukemia

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Between 1988 and 1992, seven patients with overt meningeal leukemia who had received adequate central nervous system (CNS) prophylaxis were treated with intermittent craniospinal irradiation and intrathecal methotrexate (IIIC). Follow-up time ranged from 8 months to 41 months with median of 20 months. Three of 7 patients developed subsequent CNS relapse. CNS remission durations were 8, 9, 13, 20, 28, 34, 36 months from diagnosis of CNS leukemia for which IIIC was given. Disease free survival after CNS relapse ranged from 2 to 36 months with median of 11 months. Overall survival after CNS relapse ranged from 8 to 41 months with median of 28 months. Five patients died of sepsis and bleeding secondary to bone marrow relapse. Two patients are alive at present. But they developed recurrent CNS disease 10 to 11 months after completion of IIIC. To improve the outcome, modification of IIIC by reduction of rest period and prolonged administration of intrathecal chemotherapy after completion of IIIC are required.

Key Words: Acute lymphocytic leukemia, Meningeal relapse, Intermittent craniospinal irradiation

INTRODUCTION

Overt meningeal relapse in acute lymphocytic leukemia (ALL) has been dramatically diminished by prohylactic treatment of subclinical disease early in course of therapy. Even with most effective form of treatment, 5% to 10% of ALL patients evidence primary failure in the central nervous system (CNS)[1]. Treatment of overt CNS leukemia has been considerably less successful. Especially in a small number of patients who develop overt CNS leukemia following adequate dose of cranial irradiation, the survival is very poor[2,3]. Also the quality of life is frequently compromised from the late CNS effect of repeated radiation and intrathecal medication[4].

In attempt to improve the survival and to reduce the late effect of treatment in these paients we start a protocol (IIIC) using intermittent CNS irradiation in conjunction with intrathecal chemotherapy based on experience by Kim et al[5]. Following is the preliminary report of first 7 patients treated according to this protocol.

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MATERIALS AND METHODS

Between August 1988 and May 1992, seven patients with recurrent CNS leukemia who had received adequate CNS prophylaxis, entered the study at St. Mary's Hospital. Patients characteristics, prognostic factors, course of disease and treatment are summerized in table 1. Criterion of diagnosis of CNS leukemia was the finding of leukemic cell in any number on a cerebrospinal fluid (CSF) cell count. Initially patients were treated with triple intrathecal chemotherapy composed of methotrexate, cytosine arabinoside and solucortef until CSF is free of leukemic cells. When CNS remission was achieved, patients then received 150 cGy to the brain and 75 cGy to the spine for three consecutive days. intrathecal methotrexate (8-12 mg/M^2) was given on the first day of irradiation. This was followed by one fraction of craniospinal irradiation (150 cGy to brain and 75 cGy to spine) every 8 weeks. Intrathecal methotrexate was given on the same day in the patients who received radiation. The planned total treatment dose is 2400 cGy to the brain and 1200 cGy to the spine. The patients were treated with 6 MV linear accelerator (SAD 100). Ther whole brain was irradiated through

opposed bilateral cranial fields, the spinal cord was included in direct posterior potals down to the level of S2, covering the meningeal sac in its entirety. Occasionally, two posterior portals were necessary to cover the spine because of the height of the patients. Paricular care was taken to cover the base of brain and orbital region, except for the lens. The radiation dose was calculated at the midplane of the brain and at the appropriate depth of the spinal cord depending on the size of patient. The planned total treatment time is 26 months. During the course of these treatment, portals were changed every 6 to 10 months in order to adjust to individual bone growth.

RESULTS

Six patients had received previous radiation as a CNS prophylaxis with doses ranging between 1800 cGy and 2400 cGy. Intrathecal methotrexate was

Table 1. Patients Characteristics, Course of disease and Treatment

Patient number	Age at Dx FAB	Initial WBC count	CNS prophylaxis	IIIC brain spine	Systemic chemotherapy during IIIC	Course of disease	Current status Cause of death CNS disease status
1	6 L1	2800	PCI 1800 cGy 3'IT×5 (MTX 12 mg, Ara-C 24 mg, SC 24 mg)	1950 cGy 975 cGy IT MTX×13	MACOP-B VCR, MTX, L-ASP	88/8 CNS relapse 88/9 1st BM relapse 89/7 2nd BM relapse	90/6 died of sepsis CNS: remission
2	4 L1	34500	PCI 2400 cGy IT MTX 12 mg×7	2400 cGy 1200 cGy IT MTX×16	MACOP-B VCR, DX pulse	88/2 1st CNS relapse 90/3 2nd CNS relapse 93/3 3rd CNS relapse	93/6 alive CNS; relapse following IIIC
3	5 L1	14800	PCI(−) 3'IT×5 (MTX 15 mg, Ara-C 30 mg, SC 30 mg)	2400 cGy 1200 cGy IT MTX×16	MACOP-B VCR, DX pulse MTX, LCV	89/12 1st CNS relapse 92/10 2nd CNS relapse 93/1 BM relapse	93/6 alive CNS; relapse following IIIC
4	4 L2	51200	PCI 1800 cGy IT MTX 12.5 mg×8	600 cGy 300 cGy IT MTX×4	MACOP-B VCR, DX pulse MTX, LCV ADR, ARA-C, VMA	91/7 Testicular relapse 91/8 1st BM relapse 92/3 CNS relapse 92/6 2nd BM relapse	92/9 died of sepsis CNS; remission
5	6 L2	20500	PCI 1800 cGy IT MTX 12.5 mg×5	1200 cGy 600 cGy IT MTX×8	MACOP-B VCR, DX pulse	90/11 1st CNS relapse 90/52nd CNS relapse 91/9 3rd CNS relapse 92/3 4th CNS relapse BM relapse	92/9 died of sepsis CNS; relapse during IIIC
6	16 L1	58900	PCI 1800 cGy IT MTX 12.5 mg×5	900 cGy 450 cGy IT MTX×6	6MP, MTX VCR, DX pulse Cytoxan, ARA-C	91/8 CNS relapse 92/3 BM relapse	92/4 died of sepsis & DIC CNS; remission
7	28 L2	119200	PCI 1980 cGy 8'IT×5(MTX 15 mg, Ara-C 50 mg, SC 50 mg)	1050 cGy 525 cGy IT MTX×7	MVP-A	89/3 testicular relapse 89/4 CNS relapse 91/5 BM relapse	91/8 died of bleeding CNS; remission

*FAB: French-American-British classification for ALL
*PCI: prophylactic cranial irradiation
*IT MTX (intrathecal methotrexate): 4 times for 2 weeks in conjunction with PCI then repeat every 5~6 months for 2 years
*3' IT (triple intrathecal chemotherapy: methotrexate, cytosine arabinoside, solucortef): 5 times for 9 days
*VCR: vincristine, MTX: methotrexate, L-ASP: L-asparaginase, DX: dexamethasone, LCV: leukovorin, ADR: adriamycin, 6-MP: 6-mercaptopurine
*MACOP-B: methotrexate, adriamycin, cyclophosphamide, vincristine, prednisolone, bleomycin
*MVP-A: methotrexate, vincristine, prednisolone, L-asparaginase

combined in four patients and triple intrathecal chemotherapy was combined in two patients. Remained one patient received triple intrathecal chemotherapy alone.

Age at the time of initial diagnosis of ALL ranged from 4 years to 28 years with median of 6 years. Disease free interval from CNS prophylaxis to first CNS relapse ranged from 6 months to 33 months with median of 11 months. Follow-up time was calculated from the date of diagnosis of overt CNS leukemia for which the IIIC was given. Follow-up time ranged from 8 months to 41 months with median of 20 months. Three of 7 patients developed second CNS relapse. CNS remission durations were 8, 9, 13, 20, 28, 34, 36 months (median 20 months) from diagnosis of CNS leukemia for which IIIC was given. Disease free survival after CNS relapse ranged from 8 to 41 months with median of 28 months (Table 2).

Six bone marrow relapse as the next adverse event interrupted the clinical remission. Five of these patients died of sepsis and bleeding. CNS disease was controlled at that time of death in four of these 5 patients. Two of the 7 patients are alive at present. But they experienced subsequent CNS relapse at 10 and 11 months following completion of IIIC (Table 1).

Patient number 1 developed bone marrow relapse and died of sepsis before the completion of IIIC (1950 to brain and 975 to spine). CNS disease was controlled at that time of death.

Patient number 2 had completed full courses of IIIC. He had history of first CNS relapse at 19 months after prophylactic cranial irradiation and had been treated by triple intrathecal chemotherapy alone. One year later, he developed second CNS relapse and received IIIC for 26 months. At eleven months after completion of IIIC, he was found to have third CNS relapse. Following triple intrathecal chemotherapy, he is well-being without evidence of CNS disease.

Patient number 3 also had completed full course of IIIC. Ten months after completion of IIIC, second CNS relapse was developed. Recurrent CNS disease was controlled by triple intrathecal chemotherapy. But he was found to have bone marrow relapse at 3 months following second CNS relapse. At present, he is on systemic reinduction.

Patient number 4 had experienced early testicular and bone marrow relapse prior to CNS relapse. He had received testicular irradiation with dose of 2400 cGy and reinduction chemothrapy. His IIIC was discontinued at 600 cGy to brain and 300 cGy to spine because of second bone marrow relapse. He received aggressive systemic chemotherapy, and died of sepsis at seven months following last IIIC.

Patients number 5 had received triple intrathecal chemotherapy alone at that time of first CNS relapse. After six months, she had experienced second CNS relapse. and subsequently underwent IIIC. White cell count was 2900/mm^3 in CSF study at that time of second relapse. CSF pleocytosis was waxing and waning during the IIIC. When she developed bone marrow relapse. IIIC was stopped at 1200 cGy to brain and 600 cGy to spine. She died of sepsis and bleeding.

Treatment to patient number 6 was ceased at 900 cGy to brain and 450 cGy to spine when she was found to have bone marrow relapse. Two

Table 2. Treatment Outcome for IIIC

Number of patient	CCSG prognostic criteria	Interval from PCI to 1st CNS relapse (months)	Duration of follow-up (months)	Duration of CNS remission (months)	Disease free survival after CNS relapse (months)	Overall survival after CNS relapse (months)
1	intermediate	8	20	20	2	22
2	intermediate	19	39	36	36	39
3	intermediate	33	41	34	34	41
4	poor	36	9	9	3	9
5	intermediate	11	28	13	11	28
6	poor	6	8	8	8	8
7	poor	9	28	28	25	28
Median (months)		11	28	20	11	28

*CCSG (Children's Cancer Study Group) prognostic criteria[27]

Good prognosis: WBC below 1000/μl and 3~6 years of age at diagnosis.

Intermediate prognosis: WBC 10000~50000/μl and any age, or WBC gelow 10000/μl and less than 3 years or greater than 6 years of age.

Poor prognosis: WBC above 50000/μl and any age.

months following the last IIIC, she died of fungemia and disseminated intravascular coagulation.

Patient number 7 was 28 years old man. Initial white cell count was very high (119200/μl with 100% of blast). Nine months after the first complete remission in bone marrow, he had experienced testicular relapse and received testicular irradiation with dose of 2500 cGy. One month following testicular relapse, he was found to have CNS relapse. Then he received intrathecal and systemic reinduction chemotherapy. IIIC was combind when CSF was free of leukemic cell. Bone marrow relapse was developed one year following CNS relapse. After that, he developed facial palsy and ptosis. But CSF was clear and MRI showed nonspecific finding. IIIC was discontinued at 1050 cGy to brain and 525 cGy to spine because of his death of bleeding.

The IIIC was well tolerated with very minimal acute reaction. Mild nausea was controlled by antiemetics. During the course of treatment, most of the patients experienced the episode of myelosuppresion resulting from intensive systemic chemothrapy. But none of patient was interrupted from IIIC due to this problem and IIIC did not disturb the ability to deliver the prescribed systemic chemotherapy on time.

The duration of follow-up ranging from 8 to 41 months was not long enough to permit evaluation of the degree, if any, of late CNS toxicity for long term survivor. Patient number 2 previously had received 2400 cGy to whole brain and received additional 2400 cGy by IIIC. His intelligence quotient was average level (point 103) at 29 months after IIIC and 48 months after prophylactic cranial irradiation.

DISCUSSION

Despite the success of CNS preventive therapy is dramatically reducing the incidence of CNS recurrence, CNS relapse remains a significant cause of treatment failure in ALL. Although CNS remissions can be induced in greater than 90% of patients, the median duration of remission is usually relatively short, ranging from 1 to 2 years. The majority of patients eventually encounter either subsequent CNS relapse or recurrence at other site such as the bone marrow or testis, or both[2,6].

The most successful treatment regimens have used intrathecal chemotherapy for CNS remission induction followed by consolidation therapy with either craniospinal irradiation or maintenence chemotherapy[7~11]. Intrathecal chemotherapy alone induces CNS remissions in more than 90% of patients; however, unless followed by maintenence intrathecal chemotherapy or craniospinal irradiation, relapse occurs in 3 to 4 months[12,13]. Craniospinal irradiation, at doses of 2400 to 3000 cGy to whole brain and 1200 to 1800 cGy to the spinal axis, is usually administered after successful induction of CSF remission[8,9,14]. To some extent, the choice of therapy for patient with overt CNS leukemia is guided by the type of CNS preventive therapy received previously. Approximately one third of patients whose initial CNS preventive therapy did not include cranial irradiation will achieve prolonged disease free survival when craniospinal irradiation is administered following reinduction of CSF remission at the time of inital CNS relapse. The Medical Research Council demonstrated a long term complete second remission rate of 30 to 50% in patients whose CNS relapse occurs after inadequate CNS prophyaxis[5].

In contrast, the role of craniospinal irradiation to treat CNS recurrence in a patient who originally received cranial irradiation as a part of CNS prophyaxis is less clear. The median survival after this type of CNS relapse has been reported to be less than 1 year and eventual survival rate less than 25%[16]. Result from the British Medical Research Council Concord and UKALL I trials demonstrated a continuous complete remission rate of less than 10% in such a patient[15]. More recently, other investigators have demonstrated substantially better results with this approach. However craniospinal irradiation administered in this setting is known to pose a significantly greater risk for delayed neurotoxicity[9].

Investigators in Detroit showed that low dose intermittent irradiation to craniospinal axis given with intrathecal methotrexate was very effective in preventing and reducing the incidence of CNS leukemia, with minimal side effect and no increased incidence of disease relapse once the therapy was discontinued[17,18]. Based on these experiences, Kim et al modifed their treatment regimen by giving a loading dose of radiation at initial phase of treatment to reduce the number of leukemic cells in the CNS more effectively. To minimize late effects on the spine, the dose of spinal radiaion was reduced to half the dose to brain. They reported excellent results for nine patients treated with this protocol (IIIC). Actuarial incidence of CNS recurrence is only 11% and actuarial disease free survivial after onset on CNS relapse is 63% at 9 years[9].

In contrast, our series had poor outcome with

same treatment protocol. Actuarial incidence of CNS recurrence is 43% at 41 months. Two survivors were found to have subsequent CNS relapse at 10 months and 11 months following completion of IIIC, respectively.

The radiobiologic and pharmacologic rationale of IIIC is not clear. Kim et al suggested four possible explanations. First, intrathecal methotrexate and craniospinal irradiation may interact synergistically to kill leukemic cells more effectively than the additive effects of both modalities used seperately[19]. Second, the excretion of methotrxate from CSF was found to be significantly delayed in patients who had CNS leukemia[12,20] and the blood brain barrier disturbance sustained by radiation can persist for months and up to years[19]. These phenomena may be increase the therapeutic effect of IIIC. Third, for leukemic cells, there may be little or no repair of sublethral damage during the 8 weeks interval between each treatment session. Forth, CNS leukemia may arise from the reseeding of leukemic cells from the bone marrow or other sites, and wide field irradiation and intrathecal medication may reduce the source of leukemic cells to the CNS[5].

But Uckan et al recently showed that a distinct initial shoulder was present on the radiation survival curves of leukemic progenitor cells in 50% of all analyzed ALL patients. They suggested that a marked heterogeneity existed in the radiobiological features of leukemic progenitor cells with a remarkable radioresistance and radiation damage repair capacity in some ALL patients and an acute radiosensitivity in the absence of a detectable repair capacity in others[21~24]. The radioresistance of leukemic cell and their ability to repair sublethral radiation damage might explain our disappointingly high relapse rate and poor survival outcome following intermittent treatment program. The rest period of 8 weeks might be too long to avoid the chance of sublethral damage repair. Especially, leukemic cells in heavily treated high risk ALL patients may be resistant to radiation therapy and chemotherapy. One patient had developed recurrent CNS disease during IIIC course and died of concomitant bone marrow and CNS relapse.

Children with a relapse confined to the CNS as the first site of relapse who are off therapy when they relapse have the best prognosis. In the study of Kun et al, two of the five long term remitter had their CNS relapse off therapy and all had relapsed more than 16 month achieved the continuous complete remission[9]. In our series, CNS relapses occured on therapy in five patients who died of subsequent bone marrow relapse. Two survivors had experienced CNS relapse off therapy. It is not known whether this reflects a biologically more indolent leukemic subtype, or whether CNS relapse off therapy implies less drug resistance.

Ochs et al analyzed the various factors for ability to predict long-term disease free status after an isolated CNS relapse. Only two factors were predictive of long-term, continuous disease free status; initial white cell count of less than 20000/μl at the time of original diagnosis of leukemia and duration of first remission in excess of 19 months after therapy[25].

In our study, disease free interval of two survivors were 19 and 33 months, respectively. One of these two patients died of bone marrow relapse had disease free interval of less than 19 months and initial white cell count more than 20000/μl.

Four of our patients received below 1200 cGy to brain, and their CNS disease were controlled at the time of death except one. In a study by Kim et al four of 9 patients received only 1500 cGy to the brain and were doing well. They suggested that the optimum total dose did not have to be as high as 2400 cGy[5].

Clinical remissions were interrupted by subsequent bone marrow relapse in six of 7 patients. Three patients who belong to poor prognostic group by CCSG (Chilren's Cancer Study Group) criteria, developed early bone marrow relapse within 1 year after CNS relapse. Aggressive craniospinal irradiation and intrathecal methotrxate controlled CNS leukemia but could not influence the subsequent occurence of hematologic relapse, especially in poor prognostic group.

In conclusion, we experienced disappoitingly high second CNS relapse rate and poor survival outcome with IIIC protocol. Three possible explanations for these results may be included; First, three of our patients had poor prognostic criteria and three patients had experienced testicular and bone marrow relapse prior to CNS relapse. They took aggressive clinical course. Second, for leukemic cells, there are remarkable repair capacity for radiation damage in some ALL patients. Thus the rest period of 8 weeks is enough to permit sublethral damage repair especially in refractory ALL patients. Therefore, modification of IIIC with reduced rest period might improve the outcome. Third, the presence of long-term resting leukemic cells in the CNS is important obstacle to eradicating CNS leukemia. There is little information about

proliferative behavoir of leukemic cell in the CNS. Kuo et al reported the results of kinetic studies of leukemic cell in the CSF. These results indicated that a large fraction of leukemic cells in the CNS are dormant cells (i.e in G_0 or an extended G_1 phase) in which state they may remain viable for long periods without begining of DNS synthesis[26]. This might explain recurrent CNS disease in two survivors at 10 and 11 months after completion of IIIC for 26 months. Addition of maintenence intrathecal chemotherapy following completion of IIIC may induce prolonged CNS remission in long-term survivor.

We recommend continuous craniospinal irradiation, if it is possible. The IIIC is reasonable alternative treatment option in heavily treated patients with prolonged bone marrow suppression. But the number of patients in our study are small. More patients with systematic follow-up examination with modification of rest interval and addition of maintenence intrathecal chemotherapy are needed. Prospective randomized comparison with continuous craniospinal irradiation is also required.

REFERENCES

1. **Sulivan MP, Chen T, et al:** Equivalence of intrathecal chemotherapy as central nervous system prophylaxis in children with acute lymphocytic leukemia: A Pediatric Oncology Group Study. Blood 60:948-958, 1982
2. **Pizzo PA:** Acute Lymphoblastic leukemia, In Principle and Practice of Pediatric Oncology. Pizzo PA, Poplack DG, Philadelphia, J.B. Lippincott. 1989, pp 348-349
3. **Bleyer WA, Poplack DG:** Prophylaxis and treatment of leukemia in the central nervous system and other sanctuaries. Seminar in Oncology 12:131-148, 1985
4. **Meadows AT, Massari DJ, et al:** Declines in IQ scores and cognitive functions in children with acute lymphocytic leukemia treated with cranial irradiation. The Lancet 2:1015-1018, 1981
5. **Kim TH, Ramsay NK, et al:** Intermittent central nervous system irradiation and intrathecal chemotherapy for central nervous system leukemia in children. Int J Radiat Oncol Biol Phys 13:1451-1455, 1987
6. **George SL, Ochs JJ et al:** The importance of an isolated central nervous system relapse in children with acute lymphocytic leukemia. J Clin Oncol 3: 776-781, 1985
7. **Willoughby MLN:** Treatment of overt meningeal leukemia in children: Results of second MRC meningeal leukemia trial. British Med J 1:864-867, 1976
8. **Sullivan MP, Moon TE, et al:** Combination intrathecal therapy for meningeal leukemia: Two vesus three drugs. Blood 50:471-479, 1977
9. **Kun LE, Camitta BM, et al:** Treatment of meningeal relapse in childhood acute lymphoblastic leukemia.: Results of craniospinal irradiation. J Clin Oncol 2:359-364, 1984
10. **Land VJ, Thomas PRM, et al:** Comparison of maintenence treatment regimens for first central nervous system relapse in children with acute lymphocytic leukemia. A Pediatric Oncology Group Study. Cancer 56:81-87, 1985
11. **Steinherz P, Jereb B, et al:** Therapy of central nervous system leukemia with intraventricular chemotherapy and low dose neuraxis radiotherapy. J Clin Oncol 3:1217-1226, 1985
12. **Sullivan MP, Vietti TJ, et al:** Clinical investigations in the treatment of meningeal leukemia: Radiation therapy regiemens vs conventional intrathecal methotrexate. Blood 34:301-319, 1969
13. **Duttera MJ, Bleyer WA:** Irradiation, methotrexate toxicity and the treatment of meningeal leukemia. The Lancet 2:703-707, 1973
14. **Bleyer WA, Poplack DG, et al:** "Concentration × time" methotrexate via a subcutaneous reservoir: A less toxic regiemen for intraventricular chemotherapy of central nervous system neoplasm. Blood 52:835-842, 1978
15. **Wiloughby MLN:** Treatment of overt central nervous system leukemia, In Central Nervous System Leukemia: Prevention and Treatment, Mastrangelo R, Poplack DG, Riccardi R, Boston, Martinus-Nijhoff, 1983, pp 113-122
16. **Miller DR, Leikin S, et al:** Intensive therapy and prognostic factors in acute lymphocytic leukemia of childhood: CCG-141, Hemat Blood Transf 26:77-86, 1981
17. **Shapiro WR, Young DF, et al:** Methotrexate: Distribution in cerbrospinal fluid after intravenous, ventricular and lumbar injections. N Engl J Med 293:161-166, 1975
18. **Zuelzer WW, Ravindranath Y, et al:** IMFRA (intermittent intrathecal methotrexate and fractional radiation) plus chemotherapy in childhood leukemia. Am J Hema 1:191-199, 1976
19. **Stephani U, Rating D, et al:** Radiation-related disturbance of blood-brain barrier during the therapy of acute lymphocytic leukemia. The Lancet 1:1036-1037, 1983
20. **Ettinger LJ, Chervinsky OS, et al:** Pharmacokinetics of methotrexate following intravenous and intraventricular administration in acute lymphocytic leukemia and non-Hodgkin's lymphoma. Cancer 50:1676-1682, 1982
21. **Morse M, Savitch J, et al:** Altered CNS pharmacol-

ogy of methotrexate in childhood leukemia: Another sign of meningeal relapse. J Clin Oncol 3: 19-24, 1985
22. **Uckun FM, Song CW, et al:** Radiobiological features of fresh leukemic bone marrow progenitor cells in acute lymphoblastic leukemia. Cancer Res 48:5788-5795, 1988
23. **Uckun FM, Gillis S, et al:** Effects of recombinent growth factors on radiation survival of human bone marrow progenitor cells. Int J Rad Oncol Biol Phys 16:415-435, 1989
24. **Uckun FM, Min WS, et al:** Radiobiological differences between normal and leukemic human bone marrow progenitor cells, unpublished data.
25. **Ochs J, Rivera G, et al:** Factors predictive of long-term disease free survival following an isolated central nervous system relapse in childhood acute lymphocytic leukemia. Proc Amer Soc Clin Oncol 3:199, 1984
26. **Kuo AM, Yatanganas X, et al:** Proliferative kinetics of central nervous system leukemia. Cancer 36: 232-239, 1975
27. **Nesbit ME, D'Angio GJ, et al:** Effect of isolated central nervous system leukemia on bone marrow remission and survival in childhood acute lymphoblastic leukemia: A report for Children's Cancer study Group, The Lancet 27:1386-1388, 1981

= 국문초록 =

급성 임파구성 백혈병의 뇌척수액내 재발시 간헐적인 전중추신경계 방사선조사 및 척수강내 화학요법의 효과

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가톨릭대학교 의과대학 성모병원 치료방사선과에서 1988년부터 1992년도까지 적절한 중추신경계 예방요법후 뇌척수액내 재발을 경험한 급성 임파구성 백혈병 환자 7명을 대상으로 간헐적인 전중추신경계 방사선조사 및 척수강내 화학요법(IIIC)을 실시하였다. 추적관찰기간은 8개월에서 41개월이었고 그 중앙값은 20개월이었다. 7명의 대상환자중 3명이 다시 뇌척수액내 재발을 경험하였고, 중추신경계 관해유지기간은 각각 8, 9, 13, 20, 34, 36개월이었다. 무병생존기간은 2개월에서 36개월로 그 중앙값은 11개월이었다. 생존율은 8개월에서 41개월로 그 중앙값은 28개월이었다. 5명이 치료기간중 골수재발에 따른 패혈증 및 출혈로 사망하였고, 2명의 생존자는 치료종료 10개월 및 11개월째 다시 뇌척수액내 재발을 경험하였다. 치료결과를 향상시키기 위해서는 치료중 휴식기간을 단축시키고, 치료후에도 일정기간동안 척수강내 유지화학요법을 연장하여 실시하는등 치료계획의 변형이 필요할 것으로 사료되었다.