Cranial Irradiation in the Management of Childhood Leukemic Hyperleukocytosis

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Purpose : Acute leukemia with hyperleukocytosis (more than $10^5/mm^3$) is at high risk of early sudden death, usually from intracerebral hemorrhage. Emergency cranial irradiation is a relatively simple approach to solve this the problem. We summarized our experience of cranial irradiation in 24 leukemic children who presented with hyperleukocytosis.

Methods and Materials : Between 1990 and 1998, 40 children with acute leukemia presenting with hyperleukocytosis were referred for emergency cranial irradiation. Among these patients, 24 children were evaluable. There were 16 boys and eight girls, their ages ranged from 2 to 13 years (median 9.5 years). The initial leukocyte counts ranged $109,910/mm^3$ to $501,000/mm^3$. Peripheral blood smear was performed in all patients and noted the morphology of the blast. Introduction of emergency cranial irradiation was determined by the leukocyte counts (more than 100,000/mm) and the existence of the blast in peripheral blood smear. All patients were treated with intravenous hydration with alkaline fluid and oral allopurinol. Cranial irradiation started on the day of diagnosis. With 2 Gy in one fraction in 4 patients, 4 Gy in two fractions in 20 patients.

Results : The WBC count had fallen in 19 patients (83%) and no intracerebral hemorrhage occurred after irradiation. There were five cases of early deaths. Four patients died of metabolic complications, and one patient with intracerebral hemorrhage. He died 5 hours after cranial irradiation. No patient had any immediate side effect from cranial irradiation.

Conclusion : Our data suggest, that emergency cranial irradiation can be safely chosen and effective in childhood leukemic patients presenting with high leukocyte counts.

Key Words : Hyperleukocytosis, Cranial irradiation

INTRODUCTION

Hyperleukocytosis in lymphocytic or myelogenous leukemia, conventionally defined as a peripheral leukocyte count more than $10^5/mm^3$, secondary to lymphocytic or myelogenous leukemia, is a medical emergency necessitating prompt intervention. Hyperleukocytosis, which is seen in 5 10% of newly diagnosed cases of childhood leukemia, has been associated with disseminated intravascular coagulation (DIC),

hyperuricemia, hyperkalemia, and hyperphosphatemia with associated renal insufficiency.[1, 2] The most serious complication is early death, usually from massive intracerebral hemorrhage secondary to hyperviscosity. Urgent cytoreduction may be difficult to achieve because unsuitability of apheresis procedure to pediatric patients with very small blood volumes. The use of emergency cranial irradiation and intravenous hydration are simple alternative approach to solve this problem.

We summarized our institutional experience with this form of treatment in 24 leukemic children who presented with hyperleukocytosis.

MATERIALS AND METHODS

Between 1990 and 1998, 40 children with acute leukemia presenting with hyperleukocytosis were referred to Department of Therapeutic Radiology, Seoul National University Hospital for emergency cranial irradiation. Among these patients, 24 children were available for their initial medical records. There were 16 boys and eight girls and the ages at diagnosis ranged from 2 to 13 years (median 9.5 years). The leukocyte counts at diagnosis ranged between 109,910 and 501,000/mm^3. Platelet counts ranged between 16×10^3 and 432×10^3/mm^3. Peripheral blood smear was performed in all patients and noted the morphology of the blast. Introduction of emergency cranial irradiation was determined by the leukocyte counts (more than 100,000/mm) and the existence of the blast in peripheral blood smear. Bone marrow aspiration and biopsy were performed in all patients for diagnosis and 15 patients had acute lymphoblastic leukemia, six had acute myelogenous leukemia, two had chronic myelogenous leukemia and one had lymphoma-leukemia. One patient was associated with neurologic deficit already from intracerebral hemorrhage which was confirmed by CT scan.

All patients were given oral allopurinol (10 mg/kg/day #3), and hydrated intravenously with 3,000 ml/m^2/day of 5% dextrose water plus 20 mEg/L Kcl, 40 mEg/L NaCl (in case of BSA > 1 m^2), and 24 mEg/L NaHCO$_3$. Serum electrolyte and urine pH were checked every 6 hours, and adjusted with the electrolyte and NaHCO$_3$ concentration. Cranial irradiation started on the day of diagnosis with parallel opposed lateral fields using 4 MV X-ray beams encompassing the entire brain. The eyes were protected with lead blocks. The total dose to the whole brain was 4 Gy with daily fraction of 2 Gy in 2 consecutive days.

RESULTS

Twenty patients received 4 Gy in two fractions and four patients received 2 Gy in one fraction. The reasons for giving only one fraction were death on the day of cranial irradiation due to initial intracerebral hemorrhage, rapid fall of leukocyte count, start of induction chemotherapy, and deterioration of metabolic status.

When the cranial irradiation was finished, the leukocyte counts declined in all except four patients. The leukocyte counts in nine patients declined below 100,000/ mm^3. The response of cranial radiation and hydration on WBC counts was shown in Table 1.

Five deaths were observed within 1 week of cranial irradiation; one case had interacerebral hemorrhage before cranial irradiation, four cases were due to metabolic acidosis. There were no intracerebral hemorrhage, no acute toxicity after radiation therapy.

Induction chemotherapy started within 4 days after emergency cranial irradiation. Remission was achieved in 14 of 19 patients. Afterward, seven patients received prophylactic cranial irradiation as a central nervous system prophylaxis according to their treatment protocol. The introduction of early radiation therapy did not preclude completing a full course of central nervous system prophylaxis. In these 14 patients, relapse occurred in three patients, five patients were under chemotherapy, and six patients remained in remission.

DISCUSSION

Although the precise pathophysiologic basis for the intracerebral complications occurring with hyperleukocytosis in the acute leukemia patients is not completely understood, clinicophathologic reviews of the problem suggest at least two pathophysiologic events. Freireich and associates and Fritz and associates first drew attention to the prevalence of massive intracerebral hemorrhage in these patients as opposed to superficial petechial intracranial hemorrhage associated with thrombocytopenia.[3, 4] They noted the general lack of severe thrombocytopenia (platelet count less than 20,000/ mm^3). Pathologically, a high frequency of perivascular infiltration by blast cells was noted, and they speculated that

Table 1. Response of Cranial Irradiation and Hydration on the WBC Counts

Change of the WBC counts*	Number of patients
Decreased	19
0 20%	7
20 50%	7
50 100%	5
Increased	4

*WBC counts 2 days after initiation of RT/ initial WBC counts
note : one patient died 5 hours after cranial irradiation therefore follow-up CBC was performed in twenty three patients.

this infiltration led to vascular damage with subsequent massive parenchymal hemorrhage. The propensity for massive intracerebral hemorrhage seems to relate to the increased viscosity of blood. Elevation of the viscosity of whole blood has been suspected with the elevation of the leukocyte count, and this increased viscosity would contribute to sludging of leukocytes and formation of leukocyte thrombi. The fact that leukemic blasts are intrinsically less deformable than normal leukocytes may further contribute to problems at the microvascular level, where leukemic blasts could plug small capillaries and initiate leukostasis.[5] Local perivascular leukemic proliferation, vascular damage, necrosis, and massive intracerebral hemorrhage follow.[6]

Wiernik and Serpick firstly have suggested the use of cranial irradiation with 6 Gy in single fraction, which was changed to 4 Gy single fraction later, to be administered on an emergency basis in an attempt to stop local leukemic proliferation and subsequent vascular damage.[7] Their group reported no death related to central nervous system hemorrhage after the institution of a policy to irradiate the patients in blast crisis. The Mayo experience seems to confirm the beneficial effect of the cranial radiation with 4 Gy in single fraction in the pediatric age group.[6]

Despite the efficacy of cranial irradiation, the potential toxicity associated with cranial irradiation coupled with the failure of this therapy to ameliorate the extraneural complications of hyperleukocytosis has led to the development of treatment to acutely decrease the circulating blast count such as leukapheresis and exchange transfusion. These techniques appear to effectively lower the leukocyte count with mean reduction of 48% for leukapheresis and 66% for exchange transfusion,[8] however both methods are invasive, especially in children, require intensive care unit support, and time consuming in preparation of intervention. These techniques are associated with rapid rebound of circulating leukemic cells, and may be associated with substantial complications, such as symptoms of hypovolemia, dilutional thrombocytopenia. And most of all, failure to maintain adequate blood flow rates can markedly decrease the efficiency of the procedure, especially in childhood patients.[9 11]

Nelson and associates reported that three infants in whom treated with intravenous hydration, urinary alkalization, and oral allopurinol therapy produced substantial reduction of leukocyte count. The authors suggested that intravenous hydration could obviate the need for cranial irradiation or in-vasive procedures such as exchange transfusion or leukapheresis.[8]

In this study, we used the radiation dose of 4 Gy in two fractions, with the purpose of reducing potential toxicity. The effect of cranial irradiation on the reduction of WBC counts was mild. Our main purpose of cranial irradiation was the prevention of intracerebral hemorrhage. It is impressive that intracerebral hemorrhage did not occur in acute childhood leukemia cases with hyperleukocytosis after emergency cranial irradiation, although there was no control group.

CONCLUSION

Although the use of emergency cranial irradiation and intravenous hydration does not prove that the procedure prevents intracerebral hemorrhage, our favorable experience suggests that it should be considered in patients with hyperleukocytosis in childhood leukemia as one of the acute management of reducing the risk of intracerebral hemorrhage.

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.   24   .   16 ,

8   2   13 (9.5) . $109,910/mm^2$ $501,111/mm^2$

$10^5/mm^2$,   .

allopurinol   .   2

Gy   1   4 , 2   20   .

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4   1

5   .   .

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