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Acute and long-term neurological complications in children with acute lymphoblastic leukemia

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Abstract

The pattern of acute and long-term neurological complications in 133 children with acute lymphoblastic leukemia (ALL) treated with two treatment protocol was reviewed. Twenty patients developed neurological complications. Nine out of 20 patients received MRC UK ALL X and the remaining 11 received MRC UK ALL XI protocol. There was no difference of neurological complications between MRC UKALL X and UK ALL XI protocol groups. The numbers of patients who developed neurological complications during induction of remission period were 11 of 133 patients (8.2%). 122 patients were observed during the maintenance period of treatment (from 6 months to 36 months). Six out of 122 patients developed neurological complications during this period. 88 patients were followed for a period of up to 6 months after the cessation of chemotherapy, i.e., in the late period. Neurological complications were found in 3 during this period. Neurological complications rate was 4 times higher in the relapsed group than in the no relapsed group ($p<0.05$). Systemic chemotherapy (including vincristine, high-dose methotrexate) and intrathecal chemotherapy seem to be the most common predisposing factors.

Introduction

The progress made in treatment of acute lymphoblastic leukemia (ALL) of childhood is one of the successes of modern medicine. Incremental advances in treatment success span a 50-year period, during which ALL has gone from a uniformly fatal disease to one with an overall cure rate greater than 75%[1-3]. This therapeutic progress is the result of treatment advances that began with the identification of effective single agent chemotherapy in the late 1940s, followed by development of combination chemotherapy and maintenance chemotherapy in the 1950s and early 1960s and the implementation of effective central nervous system (CNS) preventive therapy in the 1960s and 1970s. Continued, gradual improvement occurred through now[4]. The treatment modalities now include combination chemotherapy, CNS-directed therapy and radiotherapy. The neurological complications are mostly peripheral neuropathy, cerebrovascular accidents and convulsion[4,5]. Common neurological complications developing after completion of ALL treatment include leukoencephalopathy and neurocognitive defects[6-8].

Material and Methods

One hundred and thirty three consecutively diagnosed children with ALL under the age of 14 year from January 2004 to December 2006 who were treated according to the MRC UK ALL X (Group A) and UK ALL XI (Group B) protocols were reviewed. The diagnosis of ALL was done by complete blood count, peripheral blood film study and bone marrow study (microscopy and immunophenotyping in some cases). Patients were stratified into high, intermediate and low risk group on the basis of clinical and laboratory findings. All patients who developed neurological symptoms during or after cessation of the chemotherapy were included in the study. Five doses of vincristine were given in 5 consecutive weeks in both the protocols during induction of remission therapy. Daunorubicin was given on first and second consecutive days in UK ALL XI protocol but in MRC X protocol it was given on day 2 and day 16. L-asparaginase was given in 9 doses in UK ALL XI protocol and 6 doses were given MRC UK X

protocol. Cranial radiotherapy (24Gy) was given between 6 to 9 weeks in both the protocols in patient with CNS manifestation.

The patients who had concomitant CNS leukemic infiltration-associated neurological complications at the time of admission were excluded. Patients with neurological symptoms according to their clinical findings were subjected to electroencephalography, electromyography, computed tomography (CT), and/or magnetic resonance imaging (MRI), lumber puncture examination to define the causes and eliminate CNS leukemia, infection or bleeding. None of the patients had history of neurological pathologies prior to the onset of ALL.

Results

The numbers of patients who developed neurological complications during induction of remission period were 11 of 133 patients (8.2%). 122 patients were observed during the maintenance period of treatment (from 6 months to 36 months). Six of 122 (4.9%) patients developed neurological complications during this period. 88 patients were followed for a period of up to six months after the cessation of chemotherapy, i.e., in the late period. Neurological complications were found in 3 (3.4%) during this period. Neurological complication rate was 4 times higher in the relapsed group than in the no relapsed group ($p<0.05$).

The most frequent complications during the treatment period included peripheral neuropathy, convulsions and meningitis. Neuropathy was detected in 8 patients. It developed after second or third dosage of vincristine. The majority of these patients had walking disability. One patient who was mistakenly administered vincristine intravenously on two consecutive days developed neurogenic bladder one day later and retention of urine and required catheterization for urination. His symptoms resolved in one week. In another patient toxicity were observed after the administration of the first dose of vincristine. He had dysarthric speech, slip of the tongue and jaw pain. His MRI was normal. His speech completely resolved in a week. EEG could not be performed at the time of complaints, but these findings led us to think that the cranial nerve toxicity was due to vincristine.

The second most frequent neurological complication diagnosed in the therapy period was convulsion. Five had focal and one had generalized seizures. MRI showed a reversible leukoencephalomalacia in a patient who had focal seizure while receiving MTX in a remission induction treatment. CT scan was performed in 3 patients. Abnormality determined by CT scan in 2 patients was cerebral ischemic infarct and was normal in one patient. EEG was documented in one patient who showed epileptogenic abnormalities or generalized voltage suppression.

In the therapy period, 3 patients with fever, vomiting, nuchal rigidity and/or convulsion were diagnosed as meningitis. The cause in two cases was thought to be as iatrogenic bacterial meningitis which occurred soon after intrathecal therapy. One suffered from viral meningitis.

Patients who presented neurological complications in the late period included focal convulsion in two and severe headache with facial paralysis in one patient due to CNS relapse.

Table I. Clinical and laboratory characteristics of 20 patients who developed neurological complications

	Group A (MRC UK ALL X)	Group B (MRC UK ALL XI)
No. of patients	9	11
Mean age at diagnosis (months)	54.9	60.3
Mean WBC count at diagnosis (mm^3)	71,855	71,190
Risk groups		
High	4	2
Low	7	5
Intermediate	1	1
Relapse types		
Bone marrow	1	1
CNS	0	1
Testis	1	0
CNS + bone marrow	1	0
Non-relapse	6	9
Radiotherapy	2	1

Discussion

In this study group, 20 (15%) patients exhibited neurological complications. The incidence of neurological complications in children with ALL varies between 3% and 13% depending on the various studies[6]. Children with ALL rather frequently experience acute or transient neurological complications during the therapy period[9-11,] Neurological complications in 17 patients developed during the therapy period and the majority of them were neuropathies. Vincristine neurotoxicity is commonly associated with mixed sensorimotor neuropathy or autonomic neuropathy; only rare cases experienced serious CNS toxicity, particularly encephalopathy, coma and cranial nerve palsy[12]. In the present study, neurological complications related to vincristine were mild and did not require a dose limitation. One patient developed dysarthria after four days of the first dosage of vincristine. In all of the patients who showed neuropathy, including the dysarthric patient, symptoms resolved within 10 days without recurrence.

Table II. Neurological and investigations data of patients

Sl. No.	Patients characteristics			Symptoms	Time of complications	EMG/CT/MRI findings
	Age (month)	Sex	WBC count at diagnosis (cmm)			
1	78	M	19,000	Walking disability	Induction of remission period	Motor neuropathy
2	130	F	23,000	Walking disability	Induction of remission period	Motor neuropathy
3	64	M	1,700	Walking disability, weakness in upper extremities	Maintenance period	Subacute polyneuropathy in motor nerve fibers
4	76	F	18,000	Walking disability	Induction of remission period	Motor neuropathy
5	26	F	47,000	Walking disability, defecation, disability	Maintenance period	Polyneuropathy
6	32	M	145,000	Weakness in upper extremity, Jaw pain, slip of tongue, dysarthric speech	Induction of remission period	Normal
7	59	F	46,000	Walking retention of urine	Maintenance period	Motor neuropathy
8	14	F	17,000	Walking disability	Maintenance period	Motor neuropathy
9	94	M	330,000	Convulsion (generalized)	Induction of remission period	Infarct in cerebellum and centrum ovale
10	65	M	21,000	Convulsion (focal)	Induction of remission period	Leukoencephalomalacia
11	184	F	260,000	Convulsion (focal)	Induction of remission period	Cerebral ischemic infarct
12	19	F	28,700	Convulsion (focal)	Induction of oremission period	Generalised voltage suppresson
13	42	F	27,000	Convulsion (focal)	Maintenance period	Cerebral ischemic infarct
14	64	M	22,000	Convulsion (focal)	Induction of remission period	Normal
15	68	F	1,400	Fever, vomiting, convulsion, nuchal rigidity	Maintenance period	Suggestive of bacterial meningitis
16	44	F	48,000	Fever, vomiting, convulsion, nuchal rigidity	Induction of remission period	Suggestive of bacterial meningitis
17	62	M	65,000	Convulsion, nuchal rigidity	Induction of remission period	Suggestive of viral meningitis
18	35	M	112,000	Convulsion (focal)	After cessations of chemotherapy	Normal
19	36	F	48,000	Convulsion(focal)	After cessations of chemotherapy	Normal
20	45	F	150,000	Headache	After cessations of chemotherapy	Normal

CT: Computed tomography; MRI: Magnetic resonance imaging; EEG: Electroencephalography; EMG: Electromyography.

The second most frequent neurological complication was convulsion. The possible etiology of convulsions was attributed to the toxicity of combined systemic and/or intrathecal therapy. MTX can cause acute or delayed neurological toxicity. Acute toxicity commonly presents with generalized seizures and change of mental status after intrathecal injection. Systemic administration can cause convulsions or a transient encephalopathy status[12]. In our study, it usually occurred after intensive chemotherapy that included high-dose MTX (1.5 g/kg/d and 2 g/kg/d in Total XI and Total XIII treatment protocols, respectively). In 3 of the 6 patients who develop convulsion, it occurred in the first year of therapy and the patients were taking a more intensive therapy because of high risk of relapse. In one patient who had focal seizure after receiving intrathecal MTX, MRI showed a reversible leukoencephalomalacia. He developed seizures at the time of injection. Although it is reported that L-asp may cause intracranial hemorrhage or thrombosis by disturbing the balance of proteins that are important for coagulation and fibrinolysis, we could not demonstrate any pathology in his radiological investigations[13]. On the other hand, in two patients who developed seizures, cerebral ischemic infarct was detected radiologically, and L-asp may have been responsible for these complications in those patients.

Meningitis in three children occurred in the therapy period. Two of the meningitis cases were considered as iatrogenic bacterial meningitis and other one was viral.

CNS directed therapy is an essential component of management of ALL in children. The main types of the structural brain damage due to radiotherapy recorded have white matter destruction, vascular damage leading to hemorrhage and calcifications and enlargement of ventricles and/or sulcus, a sign of cortical atrophy[14-17]. Three of 20 (15%) patients received at least one course of radiotherapy. Post-irradiation syndrome was determined in one of 3 patients and was compatible with reported cases in the therapy period. The symptoms lasted for one week and subsided spontaneously. Among 3 patients, cortical atrophy, cerebral white matter changes were detected in one case in late period.

In the late period, one patient presented with headache. Although headache suggests a CNS complication, in these patients, no pathology was demonstrated on cranial CT, MRI or EEG examinations. He was classified as nonspecific headache. Two patients developed focal seizure after cessation of therapy, for which no pathology could be demonstrated on CT scan or MRI evaluation. One of two patients who developed focal seizures had no relapse or cranial radiotherapy. But one had received cranial radiotherapy. Follow-up neurological status of 20 patients revealed three patients developed permanent neurological deficits including hearing and speech problems and mental retardation.

It is reported that incidence of neurological complications increases with cumulative exposure with repeated chemotherapeutics, intrathecal therapy and radiotherapy[18,19]. Neurological complications rate were 4.5 times higher in relapsed patients than in the nonrelapsed group. On the other hand, in some of the patients, detailed evaluation of neurologic complications by examination of their pre- and post-therapy periods revealed no underlying pathology.

In conclusion, this retrospective evaluation of ALL patients for neurological complications showed that neurological complications occurring during the treatment period was primarily related to vincristine and MTX and the effect was usually reversible. Iatrogenic meningitis may be an important cause of neurological complications if proper precautions during lumber puncture are not maintained.

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