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

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We reviewed the pattern of acute and long-term (during and after treatment period) neurologic complications in children with acute lymphoblastic leukemia (ALL). Among 265 patients, 40 developed neurotoxicity. Twenty-one and 19 of the patients were treated with St. Jude Total XI and St. Jude Total XIII chemotherapy protocols, respectively. There was no difference between Total XI and XIII chemotherapy protocol groups in neurotoxicity. Neurological symptoms were determined during the therapy period in 33 (82.5%) and in the late period in 7 (15%) of 40 patients. Systemic chemotherapy (including vincristine, high-dose methotrexate) and intrathecal chemotherapy seem to be the most common predisposing factors. In the study group, neurological complications in two patients were iatrogenic as a result of lumbar puncture (1 case) and due to erroneous vincristine administration on two consecutive days (1 case).

Key words: acute lymphoblastic leukemia, children, neurotoxicity.

Intensive chemotherapy in the treatment of children with acute lymphoblastic leukemia (ALL) has dramatically improved the outcome. These treatment modalities usually include vincristine, corticosteroids, methotrexate (MTX) and radiotherapy in both systemic and central nervous system (CNS) directed therapy. Despite improved outcome in ALL, antineoplastic therapy affects both malignant cells and normal cells from mild to debilitating range and all organ systems in the acute and long-term period. In the acute term, reported neurologic complications have included mostly peripheral neuropathy, cerebrovascular accidents and convulsions[1-3]. Common neurologic complications developing after completion of ALL treatment include leukoencephalopathy and neurocognitive defects[4,5]. With the increase in survival detection of these complications would be more and important. (As survival rates increase, detection of these complications grows in importance).

Material and Methods

Two hundred and sixty-five consecutive children with ALL under the age of 17 admitted to Hacettepe University, Pediatric Hematology Unit from March 1991 to May 2005 who were eligible for and treated according to the St. Jude Total XI and XIII protocols were reviewed[6,7]. The diagnosis of ALL was based on morphological, cytochemical, immunophenotypic, cytogenetic and molecular genetic analysis of bone marrow aspirates[6,7]. All patients who developed neurological symptoms during or after cessation of the chemotherapy were included in the study. The patients who had concomitant CNS leukemic infiltration-associated neurological complications were excluded. Patients with neurologic symptoms according to their clinical findings were subjected to electroencephalography (EEG), electromyography (EMG), computed tomography (CT), and/or magnetic resonance imaging (MRI), lumbar puncture and metabolic examination to define the causes and eliminate CNS leukemia, infection or bleeding. None of the patients had history due to neurological pathologies prior to the onset of ALL. At the time of analysis, therapy in three patients was continuing.

Results

In our department, between 1991 to 1997, St Jude Total XI original protocol (n=139) and from 1997 to 2005 Total XIII protocol (n=126)

with minor modification (steroid 20 mg/kg methylprednisolone at induction period) were used in ALL treatment. Twenty-one (52.5%) of 40 of the patients received Total XI and the remaining 19 (47.5%) received Total XIII treatment protocol. Characteristics of the patients are shown in Table I.

Twenty-three of 40 (57.5%) patients with neurological findings had been given cranial radiotherapy; that 17 (42.5%) of them were in higher risk group and in additional 7 (17.5%) following relapse (1 of the 7 had a second course of radiotherapy due to second relapse).

Table I. Clinical and Laboratory Characteristics of 40 Patients with Neurological Findings

Age at diagnosis (median)	72 (range 14-180 months)	
Sex (M/F) (%)	8 (20%)/32 (80%)	
WBC on diagnosis/mm^3(median)	19,900/mm^3 (range 1,700-530,000)	
Immunophenotype n (%)	Calla + B cell	19 (47.5%)
	B cell	6 (15 %)
	T cell	7 (17.5%)
	Mixed	3 (7.5%)
	Non-determined	5 (12.5%)
Risk groups	High	24 (60%)
	Low	5 (12.5 %)
	Intermediate	11 (27.5%)
Treatment regimen	St. Jude Total XI	21 (52.5%)
	St. Jude Total XIII	19 (47.5%)
Relapse types	Bone marrow	12 (30%)
	CNS	4 (10%)
	Testis	2 (5%)
	CNS+bone marrow	1 (2.5%)
	Non-relapse	21 (52.5%)
Cranial radiotherapy (n/%)	Yes	23 (57.5 %)
	No	17 (42.5%)
Outcome	Remission	12 (30%)
	No data	8 (20%)
	On treatment	3 (7.5%)
	Exitus	17 (42.5%)

CNS: Central nervous system.

The numbers of patients having neurological symptoms during remission induction, maintainance treatment and after the treatment period, i.e. in the late period, were 21 (52.5%), 12 (30%) and 7 (17.5%), respectively. The incidence of neurologic complication was 15.1% of 265 patients. This rate was 2.6% for the late period complications. Forty of 265 patients with nonrelapsed (n=220) and relapsed (n=45) ALL presented neurologic complications (n=21, 9.5% and n=19, 42.2%, respectively). Neurologic complication rate was 4.5 times higher in the relapsed group than in the nonrelapsed group ($p<0.05$). In 6, 4 and 1 of the 19 relapsed patients with neurological complications, relapses occurred 2, 3, and 4 times, respectively.

The median interval between diagnosis of ALL and appearance of neurological symptoms was 15.6 months (range 0-126). The median interval between relapse and appearance of neurological symptoms was 1.8 (range 0-11) months. The median interval between the diagnosis and relapse was 29 (1.8-69) months.

Radiological investigation with MRI (n=19) and CT scans (n=12) was performed during treatment or in the late period, according to symptomatic clinical findings of the patients. Abnormalities determined by MRI in 8 of 19 patients and by CT scan in 7 of 12 patients are shown in Table II. EEG was documented in 10 patients. All except two showed epileptogenic abnormalities or generalized voltage suppression.

Table II. Neurological and Radiological Data of Patients

Time of determination	Patient no.	Findings	Symptoms	CT	MRI	EEG	EMG
During therapy period	1	Meningitis	Nuchal rigidity	–	–	–	–
	2	Meningitis, Convulsion	Convulsion	Normal	–	–	–
	3	–	Headache	Normal	Normal	–	–
	4	Convulsion	Convulsion	–	Infarct in cerebellum and centrum ovale	Deceleration in ground activity	–
	5	Neuropathy	Walking disability	–	–	–	Motor neuropathy
	6	–	Vomiting	Bilateral occipital ischemic infarct	–	–	–
	7	–	Facial paralysis	Hydrocephaly	Normal	–	Bilateral axonal degeneration in facial nerve
	8	Intracranial hemorrhage	Headache	Multiple bleeding foci	–	–	–
	9	Convulsion	Convulsion	Frontal subdural enlargement	–	Generalized rhythm disorder	–
	10	Neuropathy	Walking disability	–	–	–	Motor neuropathy
	11	Neuropathy	Walking disability, weakness in upper extremities	–	–	–	Subacute polyneuropathy in motor nerve fibers
	12	Neuropathy	Walking disability	Cortical atrophy	–	–	–
	13	Neuropathy	Walking disability	–	–	–	Motor neuropathy
	14	Coma	Dysarthria	–	Bilateral subacute subdural hemorrhage	–	–
	15	–	Dysarthria		Normal	–	–
	16	Convulsion	Convulsion	–	Leukoencephalomalacia	Deceleration in ground activity	–
	17	Meningitis, Convulsion	Convulsion, Nuchal rigidity	Normal	–	Generalized rhythm disorder	–
	18	Neuropathy	Walking disability, Defecation disability	–	–		Axonal degeneration, Polyneuropathy
	19	Neuropathy	Weakness in upper extremities	–	Normal	–	Motor neuropathy
	20	–	Ptosis, Vomiting	–	Normal	–	Normal
	21	Neuropathy	Walking disability, Dysuria	–	–	–	Polyneuropathy
	22	Convulsion	Convulsion	Normal	–	Generalized voltage suppression	–
	23	Convulsion	Facial paralysis, Hemiparesis	Left parietal infarct	–	Generalized voltage suppression	–
	24	Neuropathy	Walking disability	–	Intensity increase in conus medullaries	–	Motor neuropathy
	25	Neuropathy	Walking disability	–	Extraaxial cerebrospinal cavity enlargement	–	Axonal degeneration, Polyneuropathy
	26	Neuropathy	Walking disability	–	–	–	–
	27	Coma, Quadriplegia	Walking disability	–	Contrast enhancement of fibers of cauda equina	–	–
	28	–	Vomiting, Visual disturbance	–	Leukoencephalomalacia	–	–

Continue next page

Table II. Neurological and Radiological Data of Patients (Continued)

Time of determination	Patient no.	Findings	Symptoms	CT	MRI	EEG	EMG
During therapy period	29	Convulsion	Headache, Vomiting, Weakness in upper extremities	–	Normal	Deceleration in ground activity	Normal
	30	Postirradiation	Headache	–	–	–	–
	31	Meningitis	Headache, Nuchal rigidity	–	–	–	–
	32	Postirradiation	Headache, Visual disturbance	–	–	–	–
	33	Postirradiation	Visual disturbance	–	Normal	–	–
After cessation of treatment	34	Convulsion	Convulsion		Normal	Generalized voltage suppression	–
	35	Convulsion	Convulsion	–	Normal	Normal	–
	36		Headache	Normal	–	–	–
	37		Headache	Tubular calcification in right internal carotid and middle cerebral arteries	Increase in white matter intensity	–	–
	38		Headache	–	Normal	–	–
	39	Convulsion	Convulsion	–	–	Normal	–
	40	Facial paralysis	Headache	–	Normal	–	–

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

The most frequent complications during the treatment period included neuropathy, convulsions and meningitis. Neuropathy was detected in 11 patients and EMG was performed in nine of them. It developed in all 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 required catheterization for urination. His symptoms resolved in one week. In another patient, toxicity was 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 neurologic complication diagnosed in the therapy period was convulsion (n=8). Six had focal and two had generalized seizures. MRI showed a reversible leukoencephalomalacia in a patient who had focal seizure while receiving MTX in remission induction treatment.

In the therapy period, four patients with fever, vomiting, nuchal rigidity and/or convulsion were diagnosed as meningitis. The cause in two was not explained and was classified as iatrogenic meningitis which occurred soon after intrathecal therapy. Two were defined as bacterial meningitis.

Patients who presented neurological complications in the late period (n=7) included generalized convulsions in three, severe headache in three and severe headache with peripheral facial paralysis in one patient.

Three of 40 patients who expressed neurological sequelae in their follow-up period are described below. One patient had hearing and speech disorder with mental and motor retardation. He has been followed for 77 months without treatment. He is now 16 years old and has a history of cranial radiotherapy as well as aminoglycoside administration in his therapy.

Another patient whose treatment had been completed for 85 months was 15 years old and had a hearing problem. Therapy in one patient with visual disturbance and mental retardation is ongoing because of the third CNS relapse. In this patient, neurological complications were not associated with CNS relapse.

While antiepileptic treatment was started in six (15%) of 40 patients, only one still required anticonvulsant treatment in the late period. The outcome of 40 patients is shown in Table I.

Discussion

In this study group, 40 of 265 (15.1%) patients exhibited neurological abnormality. The incidence of neurotoxicity in children with ALL varies between 3% and 13% depending on the various studies[3,8]. Children with ALL rather frequently experience acute or transient neurotoxicity during the therapy period. Our findings were also compatible with the literature reports[3]. Neurotoxicity in 33 patients developed during the therapy period, and the majority of events were neuropathies. As indicated in the past studies, vincristine neurotoxicity is commonly associated with mixed sensorimotor neuropathy or autonomic neuropathy; only rare cases experienced serious CNS toxicity, particularly encephelopathy, coma and cranial nerve palsy[9-11]. In our study, neurotoxicity related to vincristine and responsible for the motor problems in these children was mild and did not require a dose limitation. One patient showed dysarthria, an uncommon complication, four days after the first dosage of vincristine[10]. None of the patients was receiving itraconazole, which may enhance the neurotoxicity when used concurrently. In all of the patients who showed neuropathy, including the dysarthric patient, symptoms resolved within 10 days without recurrence.

The second most frequent neurological finding was convulsions. The possible etiology of convulsions was attributed to the toxicity of combined systemic and/or intrathecal therapy[12]. 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 encephelopathic status[2-4]. 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 eight (73%) of the 11 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. Another possible etiology of convulsion in a patient with focal seizures was intravenous L-asparaginase (L-Asp) treatment. He developed seizures at the time of injection. Although it is reported that L-Asp may cause intracerebral hemorrhage or thrombosis by disturbing the balance of proteins that are important for coagulation and fibrinolysis, we could not demonstrate any pathology in his radiologic 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.

An unusual presentation of intrathecal MTX complication was observed in a patient who developed ascending myelitis with neurogenic bladder. This patient presented an unexpected feature for ALL chemotherapy. Difficulty in urination and defecation developed within three days of the treatment and progressively increased in severity. Since therapeutic approach for his toxicity was made after he transferred to our hospital, he progressed to quadriplegia[14]. He was lost after 2.5 years of follow-up. Delayed-onset transient hemiparesis and facial palsy after intrathecal administration of MTX alone or as part of triple intrathecal chemotherapy for CNS prophylaxis were also reported[15]. One of our patients developed facial paralysis after intrathecal therapy.

Meningitis in four children occurred in the therapy period. Two of the meningitis cases were considered as bacterial meningitis and other two were iatrogenic.

Central nervous system treatment is an essential component of management of ALL in children. The main types of the structural brain damage due to the radiotherapy recorded have white matter destruction, vascular damage leading to hemorrhage and calcifications and enlargement of ventricules and/or sulcus, a sign of cortical

atrophy[16]. Twenty-three of 40 (57.5%) patients recieved at least one course of radiotherapy. Postirradiation syndrome was determined in three of 23 patients and was compatible with reported cases in the therapy period[17,18]. The symptoms lasted one week and subsided spontaneously in all patients. Among the 23 patients, cortical atrophy, cerebral white matter changes and cerebrospinal cavity enlargement were detected in one, one and two patients, respectively, in the therapy period. In the late period, only one patient had a sign of cranial radiotherapy complication with calcification of arteries and increase in white matter intensity.

In the late period, the majority of events were headache. Although headache suggests a CNS complication, in four patients with headache in the late period, no pathology was demonstrated on cranial CT, MRI or EEG examinations. They were classified as nonspecific headache. These findings suggested that after the cessation of therapy, headache should be evaluated carefully. Three generalized seizures developed after cessation of therapy, for which no pathology could be demonstrated on CT scan or MRI evaluation. Two of three who developed generalized seizures had no relapse or cranial radiotherapy history, but one had received cranial radiotherapy. Follow- up neurologic status of the 40 patients revealed three with permanent neurologic deficits including hearing and speech problems and mental motor retardation.

It is reported that incidence of neurotoxicity increases with cumulative exposure with repeated chemotherapeutics, intrathecal therapy and radiotherapy, and this was compatible with our study[19]. Neurological complication rate was 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 findings showed that neurotoxicity occurring during the treatment period was primarily related to vincristine and MTX and the effect was usually reversible. Neurotoxic deleterious effect determined in the late period was observed less often, but in some patients the outcome was permanent. Iatrogenic effect on ALL patients was observed in two (5%) in our study. The retrospective evaluation also points out that some scan examinations were conducted unnecessarily, while other patients were underevaluated.

Currently, ALL patients receiving intensive chemotherapy must be closely followed for neurotoxicity while under therapy and after the therapy period. Moreover, on follow-up, neurocognitive, psychometric and radiological evaluations after the cessation of therapy may provide a better understanding of long-term sequelae of treatment modalities in ALL.

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