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Acute neurotoxicity in children with advanced stage B-non-Hodgkin's lymphoma and B-acute lymphoblastic leukaemia treated with the United Kingdom children cancer study group 9002/9003 protocols

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Abstract

We reviewed the pattern of acute neurotoxicity in children with B-non-Hodgkin's lymphoma (B-NHL) and B-acute lymphoblastic leukaemia (ALL) treated with the UKCCSG 9002/9003 protocols. Among 175 patients, 21 (12%) developed acute neurotoxicity: 9002 protocol ($n = 11/112$) and 9003 ($n = 10/63$). There were 20 boys and the median age was 10 years. Patients with neurological symptoms due to other causes were excluded. Acute neurological symptoms developed following induction chemotherapy in 7 patients, or after a more intensive course of chemotherapy containing high-dose methotrexate ($n = 14$). Nine patients required their chemotherapy to be altered because of the acute neurotoxicity. One patient died of cerebral haemorrhage but none of the remaining six deaths was attributed to acute neurotoxicity. We conclude that acute neurotoxicity is common in children treated with the 9002/9003 protocols and tends to be transient. Intrathecal and systemic chemotherapy including high-dose methotrexate is probably the most common predisposing factor. Modification of subsequent chemotherapy is not invariably necessary.

Keywords: Acute neurotoxicity; Childhood; Advanced B-NHL; B-ALL

1. Introduction

Current treatment of children with advanced B-non-Hodgkin's lymphoma (B-NHL) or B-acute lymphoblastic leukaemia (B-ALL) has dramatically improved the outcome [1–4]. The treatment involves both systemic and central nervous system (CNS)-directed chemotherapy, which includes high-dose methotrexate and cytarabine. Despite improved outcome, there is concern about treatment-related toxicity. Acute renal and infectious complications have been well defined and remain important causes of treatment failure [1,5,6]. Acute neurotoxicity is less well described and may be secondary to the underlying lymphoma/leukaemia, or to infectious or biochemical abnormalities due to underlying disease or the chemotherapy used to treat these patients. In children with B-precursor ALL treated with intermediate-dose methotrexate and intrathecal triple therapy, acute neurotoxicity, most frequently manifested as seizures, was reported in 7.8% [7]. It is important to determine the exact cause(s) of acute neurotoxicity as it may influence subsequent management and outcome if future treatment is modified.

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Table 1
Patients' characteristics and details of treatment and follow-up

Patient no.	Age (years) at diagnosis	Sex	Diagnosis	Concurrent/prior treatment	Neurotoxicity	Treatment modification	Follow-up from diagnosis
1	11.25	M	Stage III	9002 COPADM1	Generalised seizure	None	Alive 7 years
2	14.0	M	Stage III	9002 COPADM1	Generalised seizure EEG grossly abnormal	No more intrathecal or HD-MTX	Alive 6 years
3	3.5	M	Stage III	9002 COPADM2	Blurred vision and transient visual loss CT scan normal	None	Alive 7 years
4	5	M	Stage III	9002 COPADM1	Encephalopathy (hypertensive) and respiratory arrest required ventilation MRI normal	Repeated COP and then continued as per protocol	Alive 9 years
5	10	M	Stage III	9002 COPADM1	Generalised convulsion followed by right-sided weakness	Delayed further intrathecal therapy and HD-MTX	Alive 6 years
6	4	M	Stage III	9002 COP	Convulsion and encephalopathy EEG showed encephalopathic picture Also had renal failure	Missed one HD-MTX and one dose of vincristine HD-MTX given with further chemotherapy with no problem	Alive 4 years
7	4.5	M	Stage III	9002 COPADM1	Generalised convulsions	None	Died of relapse 8 months
8	15.25	M	Stage III	9002 COPADM2	Generalised convulsions	None	Alive 5 years
9	8.5	M	Stage III	9002 COP	Generalised convulsions	None	Alive 4 years
10	13.5	M	Stage III	9002 COPADM1	Weakness of left arm	None	Alive 3 years
11	8.75	M	Stage III	9002 COPADM1	Generalised convulsions	No intrathecal therapy with COPADM 1	Alive 2 years
12	7.5	M	Stage IV with spinal cord compression	9003 COPADM2	Olfactory hallucinations secondary to temporal lobe epilepsy EEG normal	None	Alive 6 years
13	14	M	B-ALL No CNS disease	9003 COPADM1	Encephalopathy and paraplegia EEG and CT scan showed apparent demyelination Also had high MTX concentration and renal impairment	Omitted further intrathecal therapy	Died of fungal infection 5 weeks from diagnosis
14	10.4	M	B-ALL No CNS disease	9003 COP	CT scan showed left-sided cerebral haemorrhage (occipital and parietal lobes) confirmed at post mortem	None	Toxic death 3 weeks from diagnosis
15	10	M	Stage IV with CNS disease	9003 COPADM1	Generalised convulsions Had renal impairment and hypertension Required dialysis	No further HD-MTX	Toxic death 5 weeks from diagnosis
16	4.75	M	B-ALL No CNS disease	9003 COP	Disorientation and convulsions.	Omitted HD-MTX; vincristine dose was reduced in COPADM1	Died of relapse 7 months

Table 1 (*continued*)

Patient no.	Age (years) at diagnosis	Sex	Diagnosis	Concurrent/prior treatment	Neurotoxicity	Treatment modification	Follow-up from diagnosis
17	13.25	M	B-ALL with CNS disease	9003 COPADM1	Generalised convulsions CT scan normal	None	Alive 3 years
18	14	M	B-ALL No CNS disease	9003 COPADM1	Generalised convulsions	None	Alive 2.4 years
19	11.5	M	B-NHL stage IV	9003 COP	Generalised convulsions	None	Alive 7 years
20	12.75	M	B-ALL No CNS disease	9003 COP	Left-sided focal seizures CT scan normal	Delayed intrathecal and HD-MTX; Tolerated subsequent doses	Died of relapse 6 months from diagnosis
21	12	F	B-ALL No CNS disease	9003 COP	Generalised convulsions Also had renal failure	None	Toxic death 4 months from diagnosis

B-ALL, B-acute lymphoblastic leukaemia; B-NHL, B-non-Hodgkin's lymphoma; CNS, central nervous system; COP, cyclophosphamide, vincristine and prednisolone; CT, computed tomography; EEG, electro-encephalogram; HD-MTX, high-dose methotrexate; MRI, magnetic resonance imaging.

In this paper we report the clinical pattern and outcome of children with advanced stage B-NHL/B-ALL who developed acute neurotoxicity following treatment with the United Kingdom Children Cancer Study Group (UKCCSG) 9002/9003 protocols.

2. Patients and methods

We retrospectively reviewed the records of 175 patients with advanced stage B-NHL or B-ALL treated between June 1990 and March 1996 with the UKCCSG 9002 ($n = 112$) and 9003 ($n = 63$) protocols [1,2]. All patients who developed acute neurological symptoms following or during chemotherapy were included in the study. Patients' characteristics and details of treatment and follow-up are shown in Table 1. Patients with minor vincristine-related neurotoxicity and those who developed acute neurotoxicity due to causes other than chemotherapy were excluded from the study by appropriate clinical and laboratory investigations. Twenty patients were male, and ages ranged from 3.5 to 15.25 years (median 10 years). All patients received appropriate supportive care after diagnosis, which included hyperhydration with intravenous dextrose saline and allopurinol. No patient received urate oxidase. Antimicrobials, total parenteral nutrition and blood products were given as clinically indicated.

3. Results

Twenty-one patients (12%) developed acute neurotoxicity after starting or while on chemotherapy (95% confidence interval 7.6–17.8%): protocol 9002 ($n = 11$); 9003 ($n = 10$). The most common manifestation was convulsions. These were generalised in 14 patients and three developed focal convulsions. Two patients developed an encephalopathic picture, one with high blood pressure (patient 4) and one (patient 14) who suffered acute visual loss and was diagnosed with cerebral haemorrhage. The time of onset of acute symptoms varied. Seven patients developed neurotoxicity following the start of, or while on, induction chemotherapy consisting of low-dose cyclophosphamide, vincristine and prednisolone (COP) with intrathecal double therapy (methotrexate and hydrocortisone) in the 9002 protocol ($n = 2$) or triple therapy (methotrexate, hydrocortisone and cytarabine) in the 9003 protocol ($n = 5$). The majority of patients developed acute neurotoxicity during or immediately after an intensive multiagent chemotherapy regimen containing high-dose methotrexate (3–8 gm/m^2) COPADAM 1 ($n = 11$) and COPADAM 2 ($n = 3$) with frequent intrathecal double or triple therapy. Daily blood methotrexate concentrations were measured and folinic acid rescue, 15 mg/m^2 every 6 h, was commenced 24 h from the start of methotrexate

infusion and continued until the concentration of methotrexate was <0.2 μmol/l [1,2]. A high serum methotrexate was documented in one patient (patient 13) at the time of acute neurological symptoms.

Radiological investigation with magnetic resonance imaging (MRI) or computed tomographic (CT) scans documented in six patients (Table 1) failed to show a specific or focal abnormality except in one patient with cerebral haemorrhage. Electro-encephalography was documented in the notes of four patients and showed a generalised non-specific abnormality. All patients required treatment with anticonvulsants. In nine patients the chemotherapy treatment was modified or altered because of concern about their poor general condition; the other 12 patients continued on the same chemotherapy regimen with no alterations. One patient died of cerebral haemorrhage and six (five with renal impairment) of causes other than neurotoxicity. Acute neurotoxicity was transient in all survivors who subsequently completed their treatment, including those whose treatment initially required modification.

4. Discussion

Modern treatment is effective in curing the majority of children with B-NHL/B-ALL. Intensive chemotherapy regimens involving high-dose systemic methotrexate, cytarabine and intensive scheduling of intrathecal therapy are the most important contributing factors in reducing CNS and systemic relapses [1–4]. Unfortunately, acute toxicity from the underlying disease or treatment remains a major concern. Improved supportive care, awareness and the aggressive treatment of biochemical and infectious complications have reduced the rate of toxic death significantly [2,4].

In children with advanced B-NHL/B-ALL, neurotoxicity may be secondary to underlying CNS disease, associated infectious or biochemical abnormalities. In this study we reviewed chemotherapy-related acute neurotoxicity that occurred after starting or during the administration of chemotherapy; it was found to be common, affecting 12% of children treated. Generalised seizures were the most common presenting feature, occured most commonly after intensive multiagent chemotherapy that included high-dose methotrexate. Five of the seven patients who developed neurotoxicity after COP chemotherapy were on the 9003 protocol, presumably due to the extra intrathecal therapy. An interesting, but unexplained finding is that 20/21 patients who developed neurotoxicity were boys.

Methotrexate given intrathecally or systemically can cause acute or delayed neurological toxicity [7,8]. Acute methotrexate neurotoxicity commonly presents with generalised seizures and change of mental status shortly after intrathecal injection [9–11]. Systemic administration in moderate or large doses can cause convulsions or a transient encephalopathic picture [12]; the latter was encountered in two of our patients. The use of intrathecal chemotherapy and concurrent systemic methotrexate might have increased the risk of acute neurotoxicity in this study [13,14]. Renal impairment reported in five of our patients can cause delayed methotrexate clearance and might have contributed to neurotoxicity. Acute neurotoxicity may have significant consequences for a patient's outcome. Further chemotherapy may have to be delayed or altered to prevent further toxicity, as happened for nine patients in this study. There are no clear guidelines about the management of children who develop acute neurotoxicity following chemotherapy. The small number of patients in our study makes it difficult to draw firm conclusions, but delaying high-dose methotrexate or subsequent intrathecal therapy for short periods of time probably does not affect the final outcome [1]. Prolonged delay or significant dose reduction will reduce the high-dose intensity that has been a major factor in improved outcome. It is of note that 12 patients were able to tolerate further treatment without any modification and there were no major consequences. Correction of associated biochemical abnormalities or infectious complications that may predispose to convulsions is essential in the management of these patients. Studies on larger number of patients and collaboration between different international groups are encouraged so that guidelines about the management of these patients can be produced.

Indications for diagnostic imaging are unclear. CT or MRI may help to discover any local pathology or abnormality, but are usually normal. Patients in this situation who present with acute neurological dysfunction should be imaged to rule out local causes, particularly those who have other risk factors for haemorrhagic complications or those with focal neurological signs. Single-photon emission computed tomography may help to show lesions that may not be picked up on MRI [15].

In conclusion, acute neurotoxicity is common in children treated with the 9002/9003 protocols and tends to be transient with little impact on final outcome. Delaying high-dose systemic and/or intrathecal methotrexate for a short time may be necessary to avoid further neurotoxicity, but major changes in chemotherapy regimen are rarely required. The question of when to stop anticonvulsant therapy remains difficult to answer. We suggest that prolonged anticonvulsant treatment is not usually required after finishing chemotherapy. Follow-up neuropsychological studies are required to assess late effects.

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