RESEARCH ARTICLE

VINCRISTINE INDUCED NEUROTOXICITY: STUDY OF 75 CASES

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Abstract

Objective

Concern for side-effects of therapy related to treatment of childhood malignancies is becoming an increasingly important topic. In this study, we evaluated extent of vincristine (VCR) induced neurotoxicity in a group of children who underwent chemotherapy, with VCR being part of the regimen.

Materials & Methods

In this investigation, for 75 children (54% boys, 46% girls), aged between 1 to 14 (mean 6.5±4.3) years, serial weekly neurological examinations were performed; of the 75, 70 had acute lymphoblastic leukemia and 5 Wilm's tumor. All patients were on a chemotherapy protocol of at least 4 consecutive VCR (1.5mg/m^2) injections.

Results

Decreased deep tendons reflexes were seen in the Achilles reflex in 78%, and the patellar reflex in 53% of patients. Muscle weakness was found in 70% of patients, being mild in 76% of them. Four percent of patients showed severe weakness. Petosis, jaw pain, hoarseness, abdominal pain and constipation were seen in 15%, 6%, 12%, 12% and 12% respectively. Paresthesia was observed in 32 of 52 patients, over 4 years old. No cases of foot drop, urinary retention or facial nerve palsy were seen in this patient group.

Conclusion

Children on usual doses of vincristine regimen may have neuropathic side effects but most of these side effects are mild and not troublesome.

Key words: Vincristine, neuropathy, neurotoxicity, side effect.

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Introduction

As a consequence of the significant improvements in the treatment of childhood acute lymphoblastic leukemia (ALL), monitoring of the therapy related side effects has become increasingly important. Vincristine (VCR) is a key drug used in ALL chemotherapy and neurotoxicity is its most common side effect (1-4); the extent and severity of its side effects that may reduce drug administration or cause its discontinuation and also interfere with the treatment of the malignancy are important. Literature available reveals discrepancies in reports between frequency and severity of VCR side effects (5-8). This study aimed to evaluate the extent and importance of neurological side effects experienced by a population of Iranian children in the Mofid children hospital on VCR therapy during the induction phase of treatment of ALL.

Materials & Methods

In this descriptive cross sectional study, all patients with pathological confirmation of ALL or Wilm's tumor, who had undergone a chemotherapy protocol including at least four consecutive weekly VCR injections in the hematology–oncology ward of the Mofid hospital in Tehran, were enrolled; patient histories were studied in detail and complete systemic and neurological physical examinations were conducted for each. Patients with underlying neurological disease, previous history of VCR injections, relapsed disease or CNS leukemia were excluded from the study. ALL patients were divided into three risk groups, the standard, intermediate and the high risk groups. Induction of remission treatment included prednisolone (2 mg/kg/day maximum 60 mg) for 4 weeks, 4 weekly injections of VCR (1.5 mg /m^2, maximum 2 mg) 8 injections of L–Asparginase (10/000 u /m^2, twice a week), 4 intratechal injections of methotraxate, ara-C, hydrocortisone with standard dosage for all patients and 4 additional injections of adriablastin (25 mg / m^2) for the high risk patients. Patients with Wilm's tumor were treated according to the Wilm's tumor international study IV. All patients were visited and physically examined weekly by a hematology fellow and a child neurologist and the following data were collected on days 0, 7, 14, 21, 28 and 56: Deep patellar and Achilles tendon reflexes (graded based on 0 to 3 scale); lower extremity muscle weakness (graded on the 0 to 5 conventional force measuring scale), jaw pain, paresthesia, constipation, abdominal pain, urinary retention (based on patient's self report), petosis, hoarseness and facial nerve palsy (based on physical examination). Data were then analyzed by SPSS software using descriptive statistics. Numerical data are presented as mean ± standard deviation. We used the descriptive Statistics, t-test and chi square to analyze data; all the statistical analyses were done with 95% confidence interval when appropriate and $P<0.05$ was considered significant.

Results

Between June 1996 to December 1998, 99 children with acute lymphoblastic leukemia and 5 with Wilm's tumor were admitted to the hematology–oncology ward of Tehran's Mofid hospital; 29 of them were excluded from the study, 5 due to discontinuation of treatment, 8 died during the chemotherapy induction, 3 were moved to other centers and 9 were unwilling to participate in the study, leaving 75 patients, pathologically confirmed for ALL (n=70) and Wilm's tumor (n=5). Age at diagnosis ranged from 11 months to 14 years (mean 6.5±2.3 y); 41(54 %) were male and 34(46 %) female. None of them had any focal neurologic deficit or malignant central nervous system involvement at initiation of treatment. The time of appearance of symptoms and signs is shown in Table 1. Decreased patellar and Achilles tendon reflexes were seen in 40(53%) and 59 (78%) of patients respectively; only 5% had decreased deep tendon reflexes in day 7, whereas 54% of patients showed decreased deep tendon reflexes on day 14. Lower extremities muscle weakness was seen in 53 (70 %) of patients, which had mostly (45.5%) started from day 14 (table 2); in 76 % of these patients, muscle force was scored 4 (slight muscle weakness), whereas it was severely decreased in 2 (4%), as shown in Table 3. In 2 of the patients, profound muscle weakness, preventing them from being able to sit developed on day 28. In 5 patients muscle weakness was significantly unilateral.

Petosis was seen in 11 (15%) patients, all less than 6 years; in one, it was bilateral, starting on day 35 and continuing until day 56. In the Wilm's tumor patients in whom VCR injections continued after day 21, petosis was seen in 4 out of 5 patients. Paresthesia, as a subjective symptom, was not reliable in patients under the age of 5 years, but in the remaining it occurred in 32 of the 52 patients. Other neurologic side effects documented were jaw pain in 5 patients, hoarseness in 9, abdominal pain, without any confirmed cause, in 9 and constipation in 9. No foot drop, urinary retention or facial nerve palsy were detected. One patient had significant orthostatic hypotension from day 14 till day 45 and, in 12% of patients, abdominal pain without any proven non-neurological origin but most probably due to autonomic neuropathy, was reported (not included in study variables). No significant difference in the neurotoxic side effects

of VCR was found between boys and girls. Neuropathic symptoms and signs were more significant in children older than 4 years of than in the younger ones (p value<0.05). The only side effect which was significantly more common in younger children was petosis.

Table 1: Demographic and treatment characteristics of study participants

Parameter		Number
Sex	Male	41(%54)
	female	34(%46)
Age(yr)	0-2	7 (%9)
	2-4	16 (%21)
	4-6	14 (%19)
	6-8	15 (%20)
	8-10	8 (%11)
	10-12	8 (%11)
	12-14	7 (%9)
Diagnosis	ALL	70
	Wilms	5
ALL induction treatment	VCR 1.5 mg/m2 weekly ×4 doses Prednisolon 2mg/kg × 28 days L-Asparginase 10/000 u/m2 × 8 doses Adriablastin 25 mg/m2 ×4 doses (only high risk patients)	
Wilms tumor Treatment	international wilms tumor study IV	

Table 2 : the time of appearance of symptoms and signs of neurotoxity in study participants.

Symptom	time of appearance(day)						
	7	14	21	28	56	56<	total percentage
Decreased Achilles reflex	3(5%)	32(54%)	7(12%)	10(17)	7(12%)	-	59(100%) %78
Decreased patellar reflex	2(5%)	18(45%)	10(25%)	7(18%)	3(%7)	-	40(100) %53
Muscle weakness	_	24(45.5%)	16(31%)	4(7.5%)	6(%10.5)	3(%5.5)	53(100%) %70
Petosis	_	2(18%)	-	2(18%)	1(9%)	6(55%)	11(100%) 15%
Hoarsness	_	2(22%)	-	5(56%)	2(22%)	-	9(100%) 12%
Foot drop	_	_	_	_	_	_	_
Urinary retention	_	_	_	_	_	_	_
Facial nerve palsy	_	_	_	_	_	_	_
Constipation	_	3(33.5%)	2(22%)	3(33.5%)	1(11%)	_	9(100%) 12%
Jaw pain	5(100%)	_	_	_	_	_	5(100%) 6%
Paresthesia [> 4 years old (52 patients)]	5(13%)	20(55%)	7(19%)	5(13%)	_	_	37(100%) 71%

Table 3: Severity of muscle weakness in study participants

Muscle force	Number of patients
0	_
+	2(4%)
++	5(9%)
+++	6(11%)
++++	40(76%)

Discussion

In our study, different neurological side effects of VCR were seen in patients. Decreased deep tendon reflexes (78%) and muscle weakness (70%) were the most common side effects, whereas gross motor disturbances seen were usually less severe. Time of onset of symptoms and signs was mostly on day 14 or later, the only symptom appearing earlier being jaw pain. The type and severity of sensory motor neuropathies observed in our patients receiving VCR are similar to those reported in other studies (5). Our data shows that the drug, rather than the underlying disease, is responsible for the neuropathy because all patients had normal neurological examination initially. In this study, the neuromyopathy was not too troublesome although it developed in most patients. These results are compatible to those reported by Reindors–Messelink et al who found neurotoxicity of VCR in usual doses is tolerable(6), indicating that if the drug is effective in treating the disease, its toxic effects may be acceptable. In the De Angelis study of patients treated with VCR including regimens, moderate to severe neuropathy and myopathy were found in all patients; initially VCR impaired fine motor coordination and corticosteroids were associated with the delayed development of proximal muscle weakness; the author concluded that weakness is predictable during intensive VCR/ corticosteroid therapy(7). Although the incidence and severity of neuropathy and myopathy were higher in this study than ours, but to some degree, corticosteroid therapy could also explain the gross motor dysfunction in our patients. Haim M et al also reported peripheral neuropathy signs in all patients under treatment with VCR, in particular muscle cramp that correlated with VCR cumulative dosage(8). In his study, Vainioupaa reported fine and gross motor dysfunctions in only 18% and 30% of patients under VCR chemotherapy, with the neurologic side effects being more common in young children(9). In our study it seems than neurologic side effects are associated with the cumulative dosage, results in agreement with most previous reports; however Harrman reported motor performance is lower in VCR treated patients and is not correlated to cumulative dosage(10).

Gastrointestinal neurotoxicity including abdominal pain and constipation, and side-effects related to autonomic neuropathy, were each (abdominal pain and constipation) seen in 12% out of our patients, with approximately one-third of these effects occuring on day 7. Fortunately our patient with gastrointestinal neuropathy suffered no life-threatening effects, but there are some reports that emphasize these type of side effects could even be fatal. Autonomic neuropathy may occur in absence of somatic neuropathy. In case of abdominal pain if ileus or constipation simultaneously persists, neuropathy as the cause of abdominal pain is more suspicious(11-12). We couldn't exclude the neurological side effects of triple intratechal therapy or myopathic side effects of corticosteroids in our patients. The same side effects in our small group of Wilm's tumor patients, who received no corticosteroids or intrathecal chemotherapy, emphasize that neurotoxicity is mostly due to VCR; however because of the limited number of Wilm's tumor cases, it was not statistically proven. Although triple interatechal therapy mostly results in central nervous system side effects and corticosteroids usually cause proximal myopathy rather than neuropathy, sometimes clear differentiation is not easy.

In conclusion, the neuropathic side effects of VCR are common but are not usually troublesome and can be tolerated.

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