INTRACRANIAL HEMORRHAGE DUE TO L-ASPARAGINASE THERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

L-asparaginase is widely used in the therapy of childhood and adult acute lymphoblastic leukemia (ALL) and rarely in acute myeloblastic leukemia (AML), lymphoma and other tumors. Intracranial hemorrhage or thrombosis may be associated with use of L-asparaginase. L-asparaginase shows that effect by decreasing the synthesis of coagulation proteins. Two cases which had intracranial hemorrhage during consolidation therapy for ALL will be presented. In both cases, neither during diagnosis nor during hemorrhage predisposing factors such as central nervous system leukemia, intratechal chemotherapy, cranial irradiation, thrombocytopenia, and extremely high leukocyte counts were present. On the fifth day one of the patients recovered and the other died in the 8th day.

In this paper we describe 2 patients who developed intracranial hemorrhage during L-asparaginase therapy.

Key words: L-asparaginase, Intracranial hemorrhage.
INTRODUCTION

L-asparaginase hydrolyses L-asparagine which is a nonessential amino acid. L-asparaginase is obtained from E.coli and Erwinia carotovara. L-asparaginase is used particularly in acute lymphoblastic leukemia (ALL) and in other hematological malignancies such as acute myeloblastic leukemia (AML) and lymphoma (1,2). Therapy has been associated with various forms of toxicity, including hypersensitivity, coagulation abnormalities and others (3,4).

L-asparaginase shows that effect by decreasing the synthesis of coagulation proteins (5,6). In literature, thrombosis is emphasized more than hemorrhagic complications due to L-asparaginase. This report describes two cases who developed intracranial hemorrhage showed by computed tomography (CT) during L-asparaginase (from E.coli) therapy at consolidation period (7).

Case Reports

Case 1

A 17-year-old man was diagnosed to have ALL in April 1994 at Dicle University School of Medicine, Hematology department. Postinduction, at the 3rd cycles of treatment hemorrhagic complications developed. One day before cerebral hemorrhage; physical examination, whole blood findings and peripheral blood smears were found within normal limits. On the next day the patient was hospitalized with loss of consciousness. Hematological parameters showed in table - 1, Cranial CT in figure-1.

In cerebrospinal fluid (CSF) examination a great amount of erythrocytes, 60 mg/dl protein, 60 mg/dl glucose, 100 mEq/L chlorine and negative bacterial culture were found. Chemotherapy was discontinued. He recovered on the 5th day of cessation of therapy. He remains in remission 46 months later and not receiving any therapy.

Case 2:

A 26-year-old woman was diagnosed to have ALL in July 1994 at Dicle University, School of Medicine, Hematology department. The first cycle of consolidation therapy started in August 1994. She took four dosage of L-asparaginase, at the last dosage loss of consciousness observed. The findings of whole blood and peripheral blood smear of the previous week were normal.
Hematological findings of patient at the diagnosis showed in table-1, Cranial CT in figure 2.

CSF included a great amount of erythrocytes, 65 mg/dl protein, 50 mg/dl glucose, 108 mEq/L chlorine and negative bacterial culture. Supportive therapy applied. Chemotherapy was stopped. Recovery not observed, and died on the 8th day.

Table 1: Blood and Coagulation Parameters During Consolidation Period.

<table>
<thead>
<tr>
<th></th>
<th>Case 1 (MT)</th>
<th></th>
<th>Case 2 (GK)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>During treatment</td>
<td>After cessation</td>
<td>During treatment</td>
</tr>
<tr>
<td>Hb: g/dl</td>
<td>11</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Leukocyte: x 10^9/L</td>
<td>9.4</td>
<td>6.2</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocyte: x 10^9/L</td>
<td>176</td>
<td>142</td>
<td>155</td>
</tr>
<tr>
<td>PTT:(sec)</td>
<td>52</td>
<td>35.6</td>
<td>58</td>
</tr>
<tr>
<td>PT:(sec)</td>
<td>41.5</td>
<td>11.9</td>
<td>36</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>55</td>
<td>335</td>
<td>60</td>
</tr>
</tbody>
</table>

Normal Range:
- Hb (g/dl): 13-16
- Leukocyte (x10^9/L): 5-10
- Thrombocyte (x10^9/L): 150-450
- Partial thromboplastin time (sec): 35-45
- Prothrombin time (sec): 10-13
- Fibrinogen (mg/dl): 200-400
Figure-1 (a): Computed tomography scan of the brain
(b): After recovering which showed intracranial hemorrhage

Figure-2: Computed tomography scan of the brain which showed intracranial hemorrhage.
DISCUSSION

L-asparaginase enzyme has a molecular weight of 133,000 daltons and hydrolyses L-asparagine. L-asparagine is synthesised by transamination of L-aspartic acid. In tumor cells, lacking of L-asparagine synthase, the L-asparagine can be obtained from the circulating pool of amino acids. As the L-asparaginase will decrease the amount of extracellular L-asparagine, tumor cells get use of this amino acid which neccessary for protein synthesis. But in normal cells, this synthesis may be re-done because of enzyme existence.

Hypoinsulinemia, hypoalbuminemia, hypolipoproteinemia, and hypofibrinogenemia developed and reduced the other coagulation factors especially factor IX and XI after treatment of L-asparaginase (8,9,10,11). Cerebrovascular symptoms dependent on L-asparaginase appear in two forms; either increased or normal coagulation factors-especially fibrinogen-and thrombotic cases developing by decreased Antithrombin III (AT III) and Plasminogen or decreased fibrinogen level and hemorrhagic cases developing by normal AT III and plasminogen concentration (12,13,14).

It was indicated that coagulopathy developed in treatment of acute leukemia with only vincristine and prednisone (15). Kansu et al reported that during prednisone therapy hypofibrinogenemia were developed and fibrin degradation products increased but no bleeding problems were seen (16). Al-Mondhery reported that, in two of the 4 patients whom vincristine and prednisone treatment applied, fibrinogen level decreased but Prothrombin time (PT), Partial thromboplastin time (PTT) and Thrombin time (TT) remain in normal limits (17). Ramsay et al used vincristine, prednisone, and L-asparaginase in 26 ALL cases. In these cases after cessation of L-asparaginase coagulation tests were turned to normal limits. Consequently those coagulation abnormality were found to be due to L-asparaginase (18).

In the study of Miniero et al when the patients are treated by prednisone, vincristine and L-asparaginase compared with patients treated by only L-asparaginase more common coagulopathy was observed (22). In the previously treated ALL cases, some hemorrhagic and thrombotic complications due to L-asparaginase have been reported (12,19,20,21,22,23,24).
Besides this, it is observed that extremities venous thrombosis (femoral, peroneal, saphenous vens), portal venous thrombosis developing in other systems such as fatal pulmonary embolism (25,26). In addition, osteonecrosis formation in vertebrae was notified as a result of coagulopathy (27). In protocol Linker et al, no other complications due to L-asparaginase reported except hypersensitivity, hepatotoxicity, subclavian and lower extremities venous thrombosis. Only one died because of hepatotoxicity and the others recovered due to changing the drug (instead of E-coli, Erwinia used) and using streptokinase-heparin treatment. We observed two intracranial hemorrhage in 26 ALL cases treated by Linker et al protocol between 1992-1995.

In literature, thrombosis is the most common coagulation abnormalities seen during L-asparaginase treatment. Hemorrhagic complications due to L-asparaginase are seen rarely and important for morbidity, once in 2 or 3 days the coagulation parameters (PT, PTT, Fibrinogen, Plasminogen, and AT III levels) must be measured and when necessary, fresh frozen plasma, AT III and thrombolytic therapy must be given.
REFERENCES


