Etoposide induced hepatotoxicity- A rare case report

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Abstract: Seminoma is a malignant germ cell tumor usually affecting the testicles. Treatment usually requires removal of the involved testis. Chemotherapy is recommended for patients with stage IIC or stage III seminomas. Etoposide containing regimens are used for treatment of this cancer. Here is a case of seminoma testis with sickle cell trait developing liver injury after one month of intake of tablet etoposide 50mg once daily. His bilirubin & alkaline phosphatase levels were significantly raised above normal limits after taking etoposide. After the drug was stopped patient’s bilirubin level started to decrease. Etoposide was replaced with carboplatin. Causality assessment using the WHO criteria showed that etoposide possibly caused this adverse reaction.

Keywords: Seminoma, Epipodophylotoxin, Bilirubin, Alkaline Phosphatase

INTRODUCTION

Seminoma is a malignant germ cell tumor usually affecting the testicles although it may arise from ovary, lung and mediastinum. About half of testicular germ cell tumors are seminomas. Treatment requires removal of the involved testicle. Chemotherapy is recommended for patients with stage IIC or stage III seminomas[1]. Depending upon extent and severity complete remissions are observed in 70-80% of patients[1]. Over 50% of patients achieving complete remission are cured with chemotherapy[1]. Etoposide & cisplatin (EP) together or Bleomycin, etoposide cisplatin (BEP) together are used for treatment. Among these three drugs etoposide appears to be least toxic and well tolerated by majority of patients.

Etoposide is semisynthetic derivative of podophyllotoxin. It forms a ternary complex with DNA and inhibits topoisomerase II enzyme, thus prevents religation of the DNA strands, and by doing so causes DNA strands to break causing errors in DNA synthesis and apoptosis of the cancer cell. It is used for treatment of cancers like testicular tumour, small cell and non-small cell lung cancer, non-Hodgkin’s lymphoma, gastric cancer [1].

Adverse effects of etoposide are nausea, vomiting, hypotension, hair loss, constipation, diarrhea, metallic taste, narrow suppression, anemia, and thrombocytopenia. Rare instances of liver injury have been reported in patients receiving etoposide [2].

CASE REPORT

Mr. SKP, 50yr old farmer presented to the Surgery OPD on 1st March,2015 with complaints of painless slowly increasing swelling on right side of scrotum for the last one & half year. He was non-diabetic, normotensive, euthyroid with no significant past medical history and there was no history of cancer in his family.

On examination, a tender, hard, smooth swelling (8 cm x 6 cm) was found with absence of cough impulse. Ultrasonography (USG) of scrotum revealed two well defined encapsulated hypoechoic solid space occupying lesion with tiny cystic space with partial normal parenchyma. A provisional diagnosis of testicular tumor was made. Blood investigations revealed alfa-fetoprotein (AFP) and human chorionic gonadotropin (HCG) to be normal but elevated placental alkaline phosphate (PLAP) and lactate dehydrogenase (LDH) levels. USG of whole abdomen revealed normal liver echotexture with no other abnormality or signs of metastasis. Hepatitis A, E, B, C serology was negative.

Operative excision (right sided inguinal orchiectomy) was done. Biopsy revealed spermatocytic

etoposide changed to carboplatin

He was prescribed tablet etoposide 50mg once daily for 20 days in one cycle to be repeated every month for six cycles. BEP regimen was not instituted in this patient by the treating physician due to her past experience of significant efficacy with etoposide and safety concerns of the regimen. Other supportive medicines given were iron200mg, folic acid5mg, gabapentin400mg once daily and multivitamin syrup twice daily.

On arrival for the second cycle after one month the patient complained of yellowish discoloration of eyes and skin. Liver function test(LFT) was sought and it was found to be deranged (total bilirubin-2.9 mg/dl, direct bilirubin-.1mg/dl, SGOT- 98IU/L, SGPT- 132 IU/L, ALP- 305 IU/L). USG of whole abdomen showed no sign of metastasis with normal homogenous liver. Patient was referred to Surgery OPD where he was prescribed Urso deoxycholic acid 150mg thrice daily.

The second cycle was administered. At the end of second cycle he was found to have increased jaundice (total bilirubin- 4.4 mg/dl, direct bilirubin-2.1 mg/dl, SGOT- 88 IU/L, SGPT- 92 IU/L, ALP- 319 IU/L). Repeat USG of whole abdomen was insignificant. He was referred to Medicine OPD, where he was suggested to investigate for hemoglobin electrophoresis which revealed sickle cell trait (HbS-40.5%, HbA-51.8%). He was further referred to Hematology OPD when the Hematologist suggested that sickle cell trait was not the cause of deranged LFT and advised him to continue ursodeoxycholic acid 150mg thrice daily. Other blood parameters were within normal limits.

Repeat USG of abdomen was done to check for any liver metastasis but nothing such was found. The drug was withdrawn finally & changed over to injection carboplatin (400mg/sq. mtr body surface) administered every 21 days. Thereafter, series of blood reports were done which showed gradual reduction in levels of bilirubin, aminotransferases (SGOT, SGPT) & alkaline phosphatase (ALP). Informed consent was taken from the patient and records of hematological parameters over a period of 4 months were depicted in Table [1].

Causality assessment using the WHO-UMC criteria showed that etoposide possibly caused hepatotoxicity. Causality assessment using the Naranjo Adverse Drug Reaction Probability Scale showed that etoposide possibly caused hepatotoxicity. On assessment by Modified Hartwig and Siegel scale, etoposide induced hepatotoxicity came under moderate severity.

Table 1: Hematological parameters before and after withdrawal of etoposide

<table>
<thead>
<tr>
<th>Blood parameters</th>
<th>Visit 1 10/4/15</th>
<th>Visit 2 13/5/15</th>
<th>Visit 3 11/6/15</th>
<th>Etoposide changed to carboplatin</th>
<th>Visit 4 27/6/15</th>
<th>Visit 5 20/7/15</th>
<th>Visit 6 20/8/15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb(gm%)</td>
<td>11</td>
<td>11.5</td>
<td>11.4</td>
<td>11.5</td>
<td>13</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>TLC(/cumm)</td>
<td>8200</td>
<td>7600</td>
<td>8500</td>
<td>9100</td>
<td>8000</td>
<td>6800</td>
<td></td>
</tr>
<tr>
<td>Bilirubin(Dir) mg/dl</td>
<td>1.1(0.4)*</td>
<td>2.9(1)*</td>
<td>4.4(2.1)*</td>
<td>3.7(1.1)*</td>
<td>2.8(0.8)*</td>
<td>1.6(0.4)*</td>
<td></td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>17</td>
<td>98*</td>
<td>88*</td>
<td>59*</td>
<td>51*</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>20</td>
<td>132*</td>
<td>92*</td>
<td>70*</td>
<td>60*</td>
<td>52*</td>
<td></td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>76</td>
<td>305*</td>
<td>319*</td>
<td>309*</td>
<td>219*</td>
<td>211*</td>
<td></td>
</tr>
</tbody>
</table>

Abnormal parameters = * (Bilirubin (Total and direct), ALP, SGOT, SGPT)

DISCUSSION

Etoposide is a cell cycle dependent and phase specific drug, affecting mainly the S and G2 phases of cell division. Etoposide undergoes glutathione and glucuronide conjugation which are catalyzed by GST1A1 and UGT1A1, respectively [3]. The dose of etoposide varies by indication and is adjusted for body weight and renal function.

Chemotherapy with etoposide is associated with asymptomatic and transient liver enzyme elevations, but very rare instances of clinically apparent liver injury have been reported in patients receiving etoposide. Sinusoidal obstruction syndrome and acute hepatitis, which generally has been self-limiting is observed in some instances [2]. The liver histology of etoposide hepatotoxicity has not been well understood.

However it is hypothesised that etoposide being metabolized by the microsomal P450 enzymes and inhibiting the function of CYP 3A4 and 2D6, the hepatic injury may be the result of its activation to a toxic intermediate [2].

Literature search reveals that cirrhosis has been reported almost exclusively in patients with sickle cell anemia, while only mild liver abnormalities have been associated with the sickle cell trait [4]. The altered shape of RBC in HbS favors intravascular hemolysis leading to tissue injury, which ranges from asymptomatic mild liver function test abnormalities to severe acute damage due to intrahepatic cholestasis and cholelithiasis [4]. But in this case of sickle cell trait, there was significant clinical jaundice, and hence etoposide might have contributed to this toxicity.
CONCLUSION

The hepatic injury caused by etoposide was found to be reversible on stoppage of the drug. It may be prudent to closely monitor patients on etoposide for hepatic injury until more experience is gained.

REFERENCES: