Hepatotoxicity issues associated with antineoplastic drug carmustine: A brief review

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Abstract
Hepatotoxicity refers to the abnormal liver functions or various liver disorders which are influenced by some drugs or chemicals. A number of chemotherapeutic drugs are associated with some kind of toxicity including hepatotoxicity. Nowadays, cancer patients are mostly prone to hepatic dysfunction because the liver is the primary site to metabolize chemotherapeutic drugs. Carmustine or BCNU is an antineoplastic agent which is widely used as an anticancer drug against lymphomas, myeloma and brain tumors: glioblastoma and medullablastoma. The present review presents the hepatotoxic effects of carmustine by going through the present literature. Though, it is highly effective against malignant neoplasms but its toxicity to liver makes BCNU restricted to use. A dose ranging from 1500 to 2850 mg/m² of BCNU proves fatal to the cancer patients causing hepatic necrosis. Exposure to BCNU for long term may lead to biliary cirrhosis and cholangiolsis.

Introduction
Carmustine or BCNU (1,3-Bis(2-chloroethyl)-1-nitrosourea) is a cell-cycle non-phase specific alkylating antineoplastic drug. BCNU as a single agent or in established combined therapy [1-5] with other agents has been used as a palliative therapy to treat certain types of brain tumors including glioblastoma [6], brain stem glioma, medullablastoma and metastatic brain tumors [7]. It is usually given by an infusion into a vein. Its usefulness has been limited by side effects which involves pericholangitis and intrahepatic cholestasis which in long term lead to cholangiolsis and biliary cirrhosis [8].

Carmustine is a nitrogen mustard β-chloro-nitrosourea compound which causes cross links in DNA and RNA. Chloroethylnitrosoureas are reactive compounds that are highly effective against malignant neoplasms in humans and animals [9]. It is an alkylating anticancer agent [10] and is orange yellow solid in appearance which may melt to an oily liquid. It possesses antiviral, antifungal and antibacterial properties but has not been used as anti-infectant till now. It is highly soluble in alcohol but poorly soluble in water. Figure 1 shows the chemical structure of carmustine.

Chemotherapy is known for killing cells that are rapidly dividing. Cancerous cells are remarked by their cell division as they lose mechanism known as contact inhibition which stops normal cells from infinite number of divisions. Usually drugs damage the nucleic acids of cancer cells including RNA or DNA so that their process of division may be halted. While carmustine alkylates and cross links DNA during all phases of cell cycles, resulting in disruption of DNA function; and stoppage of DNA replication, transcription and translation processes. It also binds and modifies glutathione reductase. It is highly lipophilic and can cross the blood brain barrier readily. This drug also carbamoylates proteins, including DNA repair enzymes and may stop the cancer cell from its functioning. Though it is an effective drug against cancer cells, its higher dose may prove fatal. Its hepatotoxic effects have been presented below.

Hepatotoxicity associated with BCNU
The newer chemotherapy agents have revolutionized the treatment options for a wide variety of cancers [11]. Though, carmustine is highly effective drug used in chemotherapy, but we know merits and demerits goes simultaneously. There are some adverse effects associated with it while treatment of the patients including hepatotoxicity. Myelosuppression [12] and pulmonary toxicity [2] are the other ones. The toxicity of a drug is totally dependent upon dosage manner, so is with Carmustine. If the dosage given is lesser in amount, the hepatotoxicity may be mild and reversible, but if high doses are administered, it may prove fatal. Mostly hepatotoxicity from chemotherapeutic drugs is idiosyncratic [11]. So, carmustine is a drug with cholestatic potency both in experimental animals and in humans [13]. 26% of the chemo patients were found to be suffering from hepatotoxic effects. The serum liver enzyme elevation raises the chances of acute liver injury including cholestatic hepatitis and acute veno-occlusive disease. Chemotherapy inducing hepatotoxicity may lead to increase in serum transaminases, alkaline phosphatases and bilirubin concentrates causing jaundice and portal system encephalopathy. Thus, BCNU possess high toxicity with slow recovery; thus, compromising the administration of drug in patients with progressive disease [14]. Table 1 presents the studies revealing the hepatotoxicity associated with carmustine or BCNU.

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Figure 1. Chemical structure of Carmustine
Hepatocyte cell cycle alteration [13] leads to fatal hepatic necrosis [17].

Brandes et al. [18] treated rats with BCNU (20mg/kg) in corn oil and observed hepatic necrosis or fatal hepatotoxicity in 1989. Stolzenbach and Larson [8] reported in 1991 increase and Na+ content of cytochrome P-450 has been noted which caused changes in the plasma amounts of K+ increase as an effect of cholestasis. If cholestasis prolongs, it may lead to biliary cirrhosis and cholangiolysis. The nitrosoureas carmustine are known to cause hepatotoxic lesions [13]. Trimetazidine (TMZ) is also the major effects caused by BCNU. A remarkable decrease in the content of cytochrome P-450 has been noted which caused changes in the bile acids and various proteins [20]. BCNU (20mg/kg) may result in intra-hepatic cholestasis in rats [18]. Cholestasis is characterized by a selective reduction of the bile salt independent fraction of bile flow [18]. The plasma amounts of K+ increase and Na+ decrease as an effect of cholestasis. If cholestasis prolongs, it may lead to biliary cirrhosis and cholangiolysis. The nitrosoureas carmustine are known to cause alterations in cell cycle of hepatocytes [9]. The permeability of bile tract also gets increased with BCNU in rat's body. The paracellular sucrose tends to enter bile tract through the process of diffusion or convection, resulting in hepatic lesions [13]. Trimetazidine (TMZ) is an antiangiogenic compound and its effects on liver were checked in rats in combination with BCNU. Results revealed a significant decrease in the GSH level in BCNU+TMZ treated rats. TMZ administration tends to increase GSH in BCNU+TMZ treated rats as compared to rats treated with BCNU alone. Thus, TMZ proved to be a protective agent for the liver functioning [17]. The hepatotoxic potential of BCNU gets more pronounced when it was given in combined dosage with carboplatin and cyclophosphamide [15]. The difference in the dosage range of BCNU causes different diseases like dosage ranging amidst 1500 to 2850 mg/m² leads to fatal hepatic necrosis [17].

Conclusion

Carmustine or BCNU is an antineoplastic agent which is extensively used as an anticancer drug against lymphomas, myeloma and brain tumors: glioblastoma and medullablastoma. The present review presents the hepatotoxic effects of carmustine by going through the available studies. Various hepatotoxic effects associated with carmustine may include lipoperoxidation, fluctuations in level of bilirubin, cholestasis, veno-occlusive liver diseases and hepatocyte cell-cycle alterations. A dose ranging from 1500 to 2850 mg/m² of BCNU was found to be causing hepatic necrosis. Exposure to BCNU for long term may lead to biliary cirrhosis and cholangiolysis. Conclusively, BCNU should be administered only under a proper dose regime.

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References


Table 1. Studies presenting the hepatotoxicity of carmustine or BCNU

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Author</th>
<th>Year</th>
<th>Subject/ model used</th>
<th>Dose administered</th>
<th>Observed hepatotoxic effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jones et al.</td>
<td>1989</td>
<td>Human</td>
<td>450mg/m²</td>
<td>Veno-occlusive liver disease</td>
<td>[15]</td>
</tr>
<tr>
<td>2</td>
<td>Brandes et al.</td>
<td>2004</td>
<td>Human</td>
<td>80mg/m²</td>
<td>Hepatic and pulmonary toxicity</td>
<td>[14]</td>
</tr>
<tr>
<td>3</td>
<td>Cary et al.</td>
<td>1980</td>
<td>Human</td>
<td>250mg/m²</td>
<td>Hepatocellular dysfunction</td>
<td>[16]</td>
</tr>
<tr>
<td>4</td>
<td>Phillips et al.</td>
<td>1983</td>
<td>Human</td>
<td>(600-2850 mg/m²)</td>
<td>Hepatic necrosis or fatal hepatotoxicity</td>
<td>[17]</td>
</tr>
<tr>
<td>5</td>
<td>Girgin et al.</td>
<td>2011</td>
<td>Rat</td>
<td>20mg/kg in corn oil</td>
<td>Lipoperoxidation</td>
<td>[8]</td>
</tr>
<tr>
<td>6</td>
<td>Laquerre et al.</td>
<td>1991</td>
<td>Rat</td>
<td>More than 50 mg/kg</td>
<td>Hepatocyte cell cycle alteration</td>
<td>[9]</td>
</tr>
<tr>
<td>7</td>
<td>Hoyt and Larson</td>
<td>1989</td>
<td>Rat</td>
<td>20mg/kg</td>
<td>Cholestasis</td>
<td>[18]</td>
</tr>
<tr>
<td>8</td>
<td>Krell et al.</td>
<td>1991</td>
<td>Rat</td>
<td></td>
<td>Hepatotoxic lesions</td>
<td>[13]</td>
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<tr>
<td>9</td>
<td>Nakae et al.</td>
<td>1988</td>
<td>Rat</td>
<td></td>
<td>Increased hepatotoxicity</td>
<td>[19]</td>
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<tr>
<td>10</td>
<td>Stolzenbach and Larson</td>
<td>1990</td>
<td>Rat</td>
<td></td>
<td>Changes in hepatic cytochrome P-450</td>
<td>[20]</td>
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