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Review Related On an Anticancer Drug: Carmustine

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ABSTRACT

Carmustine nitrosoureas disintegrate to produce reactive intermediates that serve as classic alkylating agents in the body. Carmustine is given intravenously. To know the correct synthesis and reactivity of the molecules, structural analysis is very important. 1-Methyl-1-Nitrosourea has been shown to have anti-tumour activity; the presentation of a 2- chloroethyl chain on a nitrogen particle with the addition of the nitroso group (CNUs) results in an increase in potency. Chloroethyl subordinates are effective in treating brain tumors due to their lipophilic nature which allows them to pass through the blood-brain barrier. In vitro and in vivo studies looked at the effects of a combination of Human Recombinant Tumour Rot Figure Alpha (rhTNF Alpha) and Carmustine BCNU on test melanoma. BCNU alone was not cytotoxic in vitro, but at all concentrations BCNU increased the harmfulness by expanding the TNF. B16 melanoma cells in murine were also affected by BCNU. The effects of BCNU on B16 melanoma were expanded by TNF at all concentrations. In vivo, BCNU and TNF, when given independently,

caused tumour development delay of B16 melanoma and of human melanoma xenografts in immune-deprived mice. The term 'hepatotoxicity' is used to describe the abnormal liver function or the various liver disorders that are affected by certain medications or chemicals. Many chemotherapy drugs are known to have some form of toxicity, including that of the liver. In this review, we will go through the literature on carmustine and discuss the effects of this drug on the liver. Carmustine is very effective against malignancy neoplasms. However, due to its toxicity to the liver, BCNU is restricted. A dose of 1500-2850mg/m2 BCNU is fatal to cancer patients causing liver necrosis. If BCNU is used for an extended period of time, it may result in biliary (belly) cirrhosis or chloangioplasty.

KEYWORDS: Anti-tumour Activity, Chloangioplasty, Alkylating Agents, Hepatotoxicity, Carbamoylating Activities

I. INTRODUCTION

BCNU (bis-chloroethylnitrosourea or carmustine) is a non-susceptible alkylation agent used on its own and in conjunction with other anti-neoplastic agents to treat a variety of cancers, including leukaemia, lymphoma, breast cancer, testicular cancer, ovarian cancer, gastric cancer, and pancreas cancer. BCNU is a nonspecific anti-cancer agent in the cell cycle phase. Treatment with BCNU has been associated with mild transient increases in serum enzyme levels and has been associated with acute liver injury (Cholestatic Hepatitis, Acute Veno-Acute Disease).

BACKGROUND

Carmustine is also known as kar mus' teen or BCNU. Carmustine is a nitrosoxide that is alkylating and is used to treat several types of leukaemia, lymphoma, and solid organ carcinoma. The nitrosourea group of compounds (bis-chloroethylnitrosourea), which exerts tumour cytotoxicity via multiple mechanisms. Carmustine also needs to be activated in the liver in order to form active intermediates that act by altering and cross-linking the purine base sequences in DNA. These active intermediates inhibit the synthesis of DNA, RNA, and protein, resulting in cell death in fast-dividing cells.

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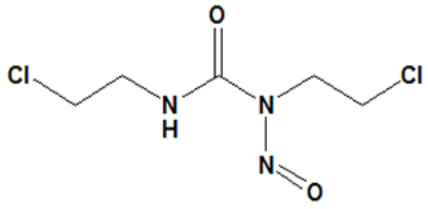
Carmustine also forms adducts with intracellular proteins. Carmustine undergoes spontaneous non-enzymatic decomposition under physiological conditions to release reactive intermediates with alkylating and carbamoylating activities, which are thought to be responsible for the antineoplastic and cytotoxic activities of carmustine. Carmustine was first approved in the US in 1977 and is currently used to treat a variety of malignancies, including breast cancer, gastric cancer, liver cancer, pancreatic cancer, lung cancer, brain cancer, ovarian cancer, testicular cancer and melanoma. It has also been approved for the treatment of Hodgkin's and Non-Hodgkin's Lymphoma and Multiple Myeloma. Carmustine is administered intravenously. It is available as a liquid (100mg vials) under the trade name Gliadel and BiCNU.

The recommended dose of Carmustine varies depending on the patient's age, weight and type of malignant disease. It is usually used in combination with anti-neoplastic drugs or used on its own in cycles of 6-8 weeks. Carmustine is also available as a gelatine wafer with 7.7mg carmustine per gelatine gelates. The gelatine gelatine gel is called Gliadel and it can be inserted into a surgical space, e.g., the brain, following the resection of high grade glioma in the brain. Toxicity Like alkylates, carmustine has some common side effects. These include: alopecia, nausea, vomiting, diarrhoea, diarrhoea gastrointestinal upset, nephrotoxicity, oral ulcers, bone marrow suppression.

Properties of carmustine

Chemical name of carmustine : 1,3-bis-(2-chloroethyl)-3-nitrosourea
Molecular formula: C5H9Cl2N3O2
Relative molecular mass: 214.05 g/mol
Structure:

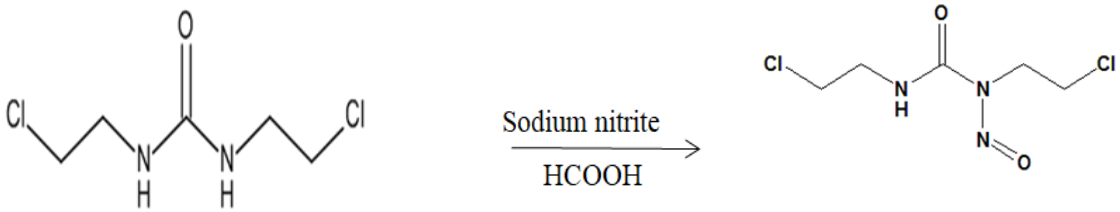


Carmustine

Carmustine appears as a light yellow granular powder. It is very slightly soluble in water and freely soluble in ethanol.

Methods of synthesis

Nitrosation of Carmustine: Carmustine is produced by the addition of sodium nitrite (sodium nitrite) via nitrosation (sodium bicarbonate) and nitrosamine (sodium chloride). The nitrosation process is carried out in acidic and cold conditions.



Carmustine

Mechanism of action

- Carmustine crosses the DNA strands by alkylation. Alkylation disrupts the function of the DNA and results in cell death.
- Carmustine also catabolizes the proteins by carbamoylating them. Carbomylating the proteins also includes enzymes such as DNA repair enzymes.
- It is highly lipophilic and easily crosses the blood brain barrier.

Structural activity relationship

- Binding with amino group will improve the oral route availability.
- Substituted phenyl group will improve oral route availability.
- Introduction of aromatic ring will improve the drug stability.
- Introduction of aromatic ring will increase the drug distribution throughout the body.
- Introduction of benzimidazole ring will provide local and fast action of the drug.
- Introducing benzimidazole will further reduce the half life of the compound.

Carmustine drug administaration and dosage available

Carmustine is a powder that is added to fluid and implanted as a wafer. The drug will be given to you by your healthcare professional. The

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dose and frequency of Carmustine injection will be determined by your physician. In general, Carmustine is used to treat brain tumors, several myeloma, and several types of Hodgkin's and Non-Hodgkin's Disease. The recommended dose of Carmustine for treatment of brain tumors is 150-200 mg / m² injected intravenously as a single dose, or divided in 2 days for every 6 weeks. Carmustine should be administered slowly and the infusion process can take up to 2 hours. The recommended dose of Carmustine for reoccurrence is 8 wafers inserted into the brain's surgical resection cavity in addition to surgery. For newly diagnosed high grade glioma in combination with surgery and radiation, the recommended dose is up to 8 wafers inserted in the brain's surgical resection cavity.

Side effects

- Nausea
- Vomiting
- CNS Facial Flushing
- Low Blood Count
- High Dosage may lead to pulmonary toxicity

Representative trade names

Carmustine – BiCNU, Gliadel®

Drug class

Antineoplastic Agents, Alkylating Agents

Complete labeling

Product labeling at DailyMed, National Library of Medicine, NIH

HEPATOTOXICITY

Serum AMINOTRASFERASE Elevations: Mild and transient abnormalities are observed in approximately 25-50% of patients receiving carmustine therapy. The mechanism of action of carmustine in conjunction with other agents is not fully elucidated. These abnormalities are usually transient, cause no symptoms, and do not necessitate dose adjustment. Clinically evident liver injury due to carmustine therapy is limited to a few cases of Cholestatic Hepatitis and more frequent cases of Sinusoidal Obstructive Syndrome. Sinusoid Obstructive Syndrome is reported mostly with high doses of carmustine or as conditioning agent prior to Haematopoetic Cell Transplantation (HCT). Sinusoid Obstruction Syndrome typically appears within 2-3 weeks after myelodysplastic myelosuppression. Symptoms of sinusoid obstruction syndrome include sudden onset of abdominal pain, weight gain, abdominal ascites, and a significant increase in Serum AMINOTransferase (and LDLH) levels, followed by Jaundice and Hepatic Dysfunction. Sinusoid obstruction syndrome ranges from a transient self-limiting injury to acute acute liver failure. Diagnosis of Sinusoidal Obstructive Syndrome is generally based on symptoms such as tenderness, enlargement, weight increase, ascites, and/or jaundice that occur within 3 weeks after chemotherapy. Liver Biopsy is a diagnostic procedure, but it is usually not recommended due to the severe involvement of thrombocytes after haematopoetic cell transplantation.

Hepatotoxicity associated with BCNU

The newer chemotherapeutic agents have changed the treatment options for many different types of cancer [11]. While carmustine is one of the most effective drugs used in chemotherapy, we know that there are pros and cons. There are some side effects associated with the treatment of the patients, including hepatotoxicity, myelosuppression, and pulmonary toxicity (2). The toxicity of any drug is completely dependent on the dosage method, and this is the case with carmustine. If the dose is low, the side effects may be reversible and mild, but if the dose is high, it may be fatal. Most of the time, the side effects of the chemotherapeutic drug are idiosyncratic. Carmustine is a cholestatic drug in experimental animals as well as in humans (13). 26% of the patients receiving carmustine were found to have hepatotoxic effects. Serum liver enzyme elevations increase the risk of acute hepatic injury including Cholestatic Hepatitis and Acute Vero-occlusive Disease. Chemotherapy that causes hepatotoxicity can increase serum transaminase, alkali phosphatase and bile circulatory concentrates resulting in Jaundice and Portal System Encephalopathy. Therefore, BCNUs have high toxicity with a slow recovery, compromising the drug administration in patients with advanced disease. Table 1 shows the studies showing the toxicity of carmustine or BCNU.

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Table 1. Studies presenting the hepatotoxicity of carmustine or BCNU

Sr. No.	Author	Year	Subject/model used	Dose administered	Observed hepatotoxic effects
1.	Jones et.al	1989	Human	450mg/m^2	Veno-occlusive liver disease
2.	Brandes et.al	2004	Human	80mg/m^2	Hepatic and pulmonary toxicity
3.	Cary et.al	1980	Human	250mg/m^2	Hepatocellular dysfunction
4.	Philips et.al	1983	Human	600-2850mg/m^2	Hepatic necrosis or fatal hepatotoxicity
5.	Girgin et.al	2011	Rat	20mg/kg in corn oil	Lipoperoxidation
6.	Laquerrieetal	1991	Rat	More than 50mg/kg	Hepatocyte cell cycle alternation
7.	Hoyt and Larson	1989	Rat	20mg/kg	Cholestsis
8.	Krell et.al	1991	Rat	------	Hepatotoxic lesions
9.	Nakae et.al	1988	Rat	------	Increased hepatotoxicity
10.	Stolzebach and Larson	1990	Rat	------	Changes in hepatic cytochrome P-450

Chemotherapy is undoubtedly a blessing for cancer patients, however, many compounds or drugs used in chemotherapy have also been shown to be toxic. In this paper, we have presented several studies with different carmustine concentrations used on rats and humans, which have been shown to cause hepatotoxicity such as lipoperoxidaemia, fluctuation in bilirubine levels, Cholestasis and veno-occclusive liver diseases, as well as alterations in the cell-cycle of hepatocytes. In some types of cancers such as leukaemia and glioblastsoma, patients are given carmustine, either alone or in combination with other agents, which may lead to liver dysfunction. In some of the patients with leukaemia who were treated with 80 mg/m2 bicarbonate of soda (BCNU), one of the patients died due to liver dysfunction after adding BCNU [14]. In another case, patients with bronchodilator carcinoma were given amoxicillin B for 3 to 4 days and BCNU for 4 days (250 mg/m2). Less than 50% of tumour area had been removed in the first three days and few patients had small cell (SCD) or large cell (CDL) carcinoma. However, one of the patients died due to liver dysfunction after adding BCNU. In addition to being a hepatotoxic agent, Amphotericin may also augment the anti-cancer properties of nitrosureas or other well-known anti-cancer agents [16].

There are also drugs that increase the hepatotoxic effects of BCNU, such as BCNU + acetaminophen. In one study, male rats were exposed to acetaminophen alone and liver necrosis was not observed. However, when BCNU was co-administered with acetaminophen, the hepatotoxic effect was increased. In some rats, BCNU was pre-administered for glutathione reuptake inhibition; this potentiated the acetaminophen hepatotoxicity induced by 3- methylcholanthrene[19]. The main effects caused by the BCNU are qualitative and quantitative changes in cytochrome p-450. A significant decrease in cytochrome pr-450 content was observed, resulting in bile acid and various protein changes [20]. BCNU may cause intra-hepsis in rats (20 mg/kg) [18]. This is due to a selective decrease of bile salt-independent fraction in bile flow (Cholestasis). Plasma levels of K+ and Na+ increase as a result of this. If this condition persists, it can lead to bile cirrhosis or cholangiopathy. Nitrosourea carmustine is known to cause changes in cell cycles of hepatocytes (9). The bile tract permeability also increases when BCNU is present in the body of rats. Paracelsus (sucrose) tends to enter the bile tract via diffusion or conduction, leading to liver lesions (13). Trimetazidin (TMZ), an anti-anginal compound, was evaluated in rats in addition to BCNU and GSH (glucose). The results

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showed a significant reduction in GSH (Glucose) in the treated rats (BCNU +TMZ). TMZ tends to raise GSH in the BCNU +TMZ treated rat compared to BCNU treated rats. Therefore, TMZ has been shown to be protective for liver function(17). BCNU has a more potent hepatotoxic effect when it is administered at a higher dose with co-administered carboplatin/cyclophosphamide [15]. The range of dosage for BCNU can lead to various diseases. For example, doses ranging from 1500mg/m2 to 2850mg/m2 can cause fatal liver necrosis [17].

Mechanism of injury

The majority of cases of carmustine hepatotoxicity appear to be dose-related and are likely to be caused by direct cytotoxic effects. Sinusoid obstruction syndrome is thought to be caused by the toxic effects of alkylators on sinusoid cells within the liver. Sinusoid cells become necrotic and secrete into the sinuses, resulting in the blocking and destruction of the liver veins. Carmustine is extensively converted by the liver's cytochrome p450 system.

Outcome and management

Liver injury caused by carmustine can range from mild increases in liver enzymes to self-limited cholestasis to severe, fatal necrosis of the liver caused by sinusoid obstruction syndrome. Currently, there is no specific treatment for veno occlusive disease aside from supportive care and prevention of rechallenge.

Drug Class: Antineoplastic Agents, Alkylating Agents

II. CONCLUSION

Carmustine (BCNU) is an anti-tumour agent that is widely used as an anti-cancer drug against lymphoma, myeloma, and brain tumors (glioblastoma, medulloblastoma, etc.). In this review, we will look at the various hepatotoxic effects caused by carmustine by reviewing the available studies. Lipoperoxidation Bilirubin level fluctuations Cholestasis Veno-occlusive Liver Diseases Hepatotoxicity Hepatocytes cell-cycle Alterations Hepatic necrosis Dose range 1500-2850mg/m2 BCNU Long-term exposure to BCNU may result in biliary Cirrhosis and chloeangiolysis Bottom line: BCNU should only be used under a proper dose regime.

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