ADVERSE REACTIONS

Pulmonary Toxicity

Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported to occur from 9 days to 43 months after treatment with Carmustine and related nitrosoureas. Most of these patients were receiving prolonged therapy with total doses of Carmustine greater than 1400 mg/m2. However, there have been reports of pulmonary fibrosis in patients receiving lower total doses. Other risk factors include past history of lung disease and duration of treatment. Cases of fatal pulmonary toxicity with Carmustine have been reported.

Additionally, delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in a long-term study with 17 patients who received Carmustine in childhood and early adolescence (1-16 years) in cumulative doses ranging from 770 to 1800 mg/m^2 combined with cranial radiotherapy for intracranial tumors. Chest x-rays demonstrated pulmonary hypoplasia with upper zone contraction. Gallium scans were normal in all cases. Thoracic CT scans have demonstrated an unusual pattern of upper zone fibrosis. There was some late reduction of pulmonary function in all long-term survivors. This form of lung fibrosis may be slowly progressive and has resulted in death in some cases. In this long-term study, 8 of 17 died of delayed pulmonary lung fibrosis, including all those initially treated (5 of 17) at less than 5 years of age.

Hematologic Toxicity

A frequent and serious toxicity of Carmustine is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks postadministration and persists for 1 to 2 weeks. Leukopenia occurs at 5 to 6 weeks after a dose of Carmustine and persists for 1 to 2 weeks. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

Carmustine may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses.

The occurrence of acute leukemia and bone marrow dysplasias has been reported in patients following long-term nitrosourea therapy.

Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

Gastrointestinal Toxicity

Nausea and vomiting after intravenous administration of Carmustine are noted frequently. This toxicity appears within 2 hours of dosing, usually lasting 4 to 6 hours, and is dose related. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect.

Hepatotoxicity

A reversible type of hepatic toxicity, manifested by increased transaminase, alkaline phosphatase and bilirubin levels, has been reported in a small percentage of patients receiving Carmustine.

Nephrotoxicity

Renal abnormalities consisting of progressive azotemia, decrease in kidney size, and renal failure have been reported in patients who received large cumulative doses after prolonged therapy with Carmustine and related nitrosoureas. Kidney damage has also been reported occasionally in patients receiving lower total doses.

Other Toxicities

Accidental contact of reconstituted Carmustine with skin has caused burning and hyperpigmentation of the affected areas.

Rapid intravenous infusion of Carmustine may produce intensive flushing of the skin and suffusion of the conjunctiva within 2 hours, lasting about 4 hours. It is also associated with burning at the site of injection although true thrombosis is rare.

Neuroretinitis, chest pain, headache, allergic reaction, hypotension, and tachycardia have been reported as part of ongoing surveillance.

OVERDOSAGE

No proven antidotes have been established for Carmustine overdosage.

DOSAGE AND ADMINISTRATION

The recommended dose of Carmustine for Injection as a single agent in previously untreated patients is 150 to 200 mg/m^2 intravenously every 6 weeks. This may be given as a single dose or divided into daily injections such as 75 to 100 mg/m^2 on 2 successive days. When Carmustine for Injection is used in combination with other myelosuppressive drugs or in patients in whom bone marrow reserve is depleted, the doses should be adjusted accordingly.

Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:

Nadir After Prior Dose		Percentage of Prior Dose to be Given
Leukocytes/mm^3	Platelets/mm^3	
>4000	>100,000	100%
3000 - 3999	75,000 - 99,999	100%
2000 - 2999	25,000 - 74,999	70%
<2000	<25,000	50%

A repeat course of Carmustine for Injection should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm3, leukocytes above 4,000/mm^3), and this is usually in 6 weeks. Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

Administration Precautions

As with other potentially toxic compounds, caution should be exercised in handling Carmustine for Injection and preparing the solution of Carmustine for Injection.

Accidental contact of reconstituted Carmustine for Injection with the skin has caused transient hyperpigmentation of the affected areas. The use of gloves is recommended. If Carmustine for Injection lyophilized material or solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Reconstituted solution should be used intravenously only and should be administered by slow intravenous infusion. Administration of Carmustine for Injection over a shorter period of time for less than 2 hours can lead to pain and burning at the site of injection.

Preparation of Intravenous Solutions

First, dissolve Carmustine for Injection with 3 ml of the supplied Sterile Diluent for Carmustine for Injection. Second, aseptically add 27 ml Sterile Water for Injection, IP. Each ml of resulting solution contains 3.3 mg of Carmustine in 10% ethanol. Such solutions should be protected from light.

Reconstitution as recommended results in a clear, colorless to yellowish solution which may be further diluted with 5% Dextrose Injection, IP. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Important Note

The lyophilized dosage formulation contains no preservatives and is not intended for use as a multiple dose vial.

Stability

Unopened vials of the dry drug must be stored in a refrigerator (2°-8°C, 36°-46°F).

Vials reconstituted as directed and further diluted to a concentration of 0.2 mg/ml in 5% Dextrose Injection, IP, should be stored at room temperature, protected from light and utilized within 8 hours.

Glass containers were used for the stability data provided in this section. Only use glass containers for Carmustine for Injection administration.

Important Note

Carmustine for Injection has a low melting point (25°C). Exposure of the drug to this temperature or above will cause the drug to liquefy and appear as an oil film on the vials. This is a sign of decomposition and vials should be discarded. If there is a question of adequate refrigeration upon receipt of this product, immediately inspect the vial in each individual carton. Hold the vial to a bright light for inspection. Carmustine for Injection will appear as a very small amount of dry powder or mass. If this is evident, Carmustine for Injection is suitable for use and should be refrigerated immediately.

Procedure for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedure recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Carmustine for Injection USP - Each package includes a vial containing 100 mg Carmustine.

STORAGE

Store between 2°C to 8°C. Protect from light.

Manufactured by

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