PRODUCT MONOGRAPH

PrCeeNU*

(Lomustine-CCNU)

Capsules: 10, 40 and 100 mg

Antineoplastic Agent

Bristol-Myers Squibb Canada
Montreal, Canada, H4S 0A4

Date of Preparation:
4 July 1974

* TM of Bristol-Myers Squibb Company
used under license by Bristol-Myers Squibb Canada

Date of Revision:
February 17, 2016

Submission control no.: 188932
PRODUCT MONOGRAPH

NAME OF DRUG

CeeNU
(Lomustine - CCNU)
Capsules; 10, 40 and 100 mg

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION: CeeNU (LOMUSTINE-CCNU) IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE TAKEN REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW IS SEEN.

ACTION AND CLINICAL PHARMACOLOGY

It is generally agreed that CeeNU (lomustine-CCNU) acts as an alkylating agent but, as with other nitrosoureas, it may also inhibit several key enzymatic processes.

CeeNU may be given orally. Following oral administration of radioactive CeeNU at doses ranging from 30 mg/m² to 100 mg/m² about half of the radioactivity given was excreted within 24 hours. The serum half-life of the drug and/or metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels at 15 minutes after intravenous administration.

Because of the high lipid solubility and the relative lack of ionization at a physiological pH, CeeNU crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50 percent or greater than those measured concurrently in plasma.
INDICATIONS AND CLINICAL USES

CeeNU (lomustine-CCNU) is indicated as palliative therapy in addition to surgery and radiotherapy or in combination therapy with other chemotherapeutic agents in the following:

1. **Brain tumors** - both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

2. **Hodgkin's Disease** – as a secondary therapy, alone or in combination with other active drugs.

**Other Tumors** – CeeNU has been used in combination with other therapeutic agents in lung cancer (squamous cell, anaplastic large cell, and adenocarcinoma), malignant melanoma and breast cancer (advanced disease) only after other conventional methods have failed.

CONTRAINDICATIONS

CeeNU (lomustine-CCNU) should not be given to individuals who have demonstrated a previous hypersensitivity to it. Also it is contraindicated in patients having severe leukopenia and/or thrombocytopenia.

WARNINGS

CeeNU (lomustine-CCNU) should be administered by individuals experienced in the use of antineoplastic therapy.

Delayed bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of CeeNU.

Blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of CeeNU should not be given more frequently than every 6 weeks.
The bone marrow toxicity of CeeNU is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see Dosage Adjustment Table under DOSAGE AND ADMINISTRATION).

Caution should be used in administering CeeNU to patients with decreased circulating platelets, leukocytes or erythrocytes (see DOSAGE AND ADMINISTRATION).

Pulmonary toxicity including pulmonary infiltration and fibrosis (often fatal) from CeeNU appears to be dose related (see ADVERSE REACTIONS).

Liver and renal function tests should be monitored periodically (see ADVERSE REACTIONS).

Concomitant use of CeeNU with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reaction of the vaccine virus because normal defense mechanisms may be suppressed by CeeNU. Vaccination with a live vaccine in a patient taking CeeNU may result in severe infection. Patient’s antibody response to vaccines may be decreased. The use of live vaccines should be avoided and individual specialist advice sought (see PRECAUTIONS, Drug Interactions).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

CeeNU is carcinogenic in rats and mice, producing a marked increase in tumour incidence in doses approximating those employed clinically.

Nitrosourea therapy does have carcinogenic potential. Long-term use of nitrosoureas has been reported to be possibly associated with the development of secondary malignancies. The occurrence of acute leukemia and bone marrow dysplasias has been reported in patients following nitrosourea therapy.

CeeNU can have a mutagenic effect. Men treated with CeeNU are therefore advised not to father children during treatment and for up to 6 months afterwards, and to seek advice regarding sperm conservation before the start of treatment given the possibility of irreversible infertility caused by CeeNU therapy. CeeNU also affects fertility in male rats at doses somewhat higher than the human dose.
Pregnancy
Safe use in pregnancy has not been established. CeeNU is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patients should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Nursing Mothers
Due to the lipophilic nature of CeeNU, it is likely to be excreted in breast milk. As a risk to the nursing child exists, a decision should be made whether to discontinue breastfeeding or to discontinue CeeNU therapy.

PRECAUTIONS

Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least six weeks after a dose.

Baseline pulmonary function studies should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70% of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DLco) are particularly at risk.

Since CeeNU (lomustine-CCNU) may cause liver dysfunction, it is recommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

Effects on ability to drive and to use machines
No studies on the effects on the ability to drive and use machines have been performed.

Drug Interactions
No drug interaction studies have been performed. It is unknown which hepatic enzymes are involved in lomustine-CCNU metabolism in humans. Animal studies suggest that CYP2C19, CYP2D6 and CYP3A4 are involved.
Drug-drug interactions of CeeNU with anti-epileptic drugs

Co-administration of some antiepileptic drugs and CeeNU can lead to complications secondary to pharmacokinetic interactions between the drugs.

Co-administration of enzyme-inducing antiepileptic drugs (e.g., carbamazepine, and phenytoin) may result in decreased blood concentration and reduced efficacy of CeeNU. Concurrent use of CeeNU with enzyme-inducing antiepileptic drugs should be avoided.

Co-administration of valproic acid or other enzyme-inhibiting drugs may impair the metabolism and increase the toxicity of CeeNU. Caution should be exercised when valproic acid and CeeNU are co-administered.

The toxic effects of valproic acid may be increased when combined with CeeNU.

Co-administration of CeeNU with phenytoin may lead to a decrease of phenytoin levels and a decrease in seizure control.

Other Interactions

There is increased risk of fatal systemic vaccine disease with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients including patients treated with CeeNU (see WARNINGS).

ADVERSE REACTIONS

1. **Gastrointestinal:** Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually lasts less than 24 hours. The frequency and duration may be reduced by the use of antiemetics prior to dosing and by the administration of CeeNU (lomustine-CCNU) to fasting patients.

2. **Hematologic Toxicity:** The most frequent and most serious toxicity of CeeNU is delayed myelosuppression. It usually occurs four to six weeks after drug administration and is dose related. Thrombocytopenia occurs at about four weeks post-administration and persists for one to two weeks. Leukopenia occurs at five to six weeks after a dose of CeeNU and persists for one to two weeks.

   Approximately 65% of patients receiving 130 mg/m² develop white blood counts below 5000 /mm³. Thirty-six percent developed white blood cell counts below 3000 /mm³. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.
CeeNU 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 have been reported in patients following long term nitrosourea therapy. Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

3. **Pulmonary Toxicity:** Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported rarely with CeeNU. Onset of toxicity has occurred after an interval of six months or longer from the start of therapy with cumulative doses of CeeNU usually greater than 1100 mg/m². There is one report of pulmonary toxicity at a cumulative dose of only 600 mg.

Over a 25 years follow-up time of 17 childhood / adolescent cancer survivors of intracranial tumors treated with a related nitrosourea, 2 (12%) died of early onset pulmonary fibrosis (between 0-3 years post treatment) and 7 (41%) died of late onset pulmonary fibrosis (between 6 and 25 years post treatment). Of the remaining eight patients, seven had radiologic and physiologic (i.e., lung function) evidence of upper zone pulmonary fibrosis. Patients treated at younger age seemed to be at greater risk of developing pulmonary fibrosis.

4. **Other Toxicities:** Stomatitis, alopecia, anemia have been reported infrequently.

Neurological reactions such as disorientation, lethargy, ataxia and dysarthria have been noted in some patients receiving CeeNU. However, the relationship to medication in these patients is unclear.

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

6. **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 CeeNU.
SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

Accidental overdose with CeeNu (lomustine-CCNU) has been reported, including fatal cases. Accidental overdose has been associated with bone marrow suppression, abdominal pain, diarrhea, vomiting, anorexia, lethargy, dizziness, abnormal hepatic function, cough, and shortness of breath.

There is no specific antidote for overdose with CeeNU. In the case of overdosage, appropriate supportive measures should be taken.

Because of the lipophilic nature of the drug, the product is not dialyzable.

DOSAGE AND ADMINISTRATION

The recommended dose of CeeNU (lomustine-CCNU) is 130 mg/m² as a single dose by mouth every 6 weeks (see SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL).

In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m² every 6 weeks.

A repeat course of CeeNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm³; leukocytes above 4,000/mm³). Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.
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:

<table>
<thead>
<tr>
<th>Nadir After Prior Dose</th>
<th>Percentage of Prior Dose to be Given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (/mm³)</td>
<td>Platelets (/mm³)</td>
</tr>
<tr>
<td>≥4000</td>
<td>≥100,000</td>
</tr>
<tr>
<td>3000 - 3999</td>
<td>75,000 - 99,999</td>
</tr>
<tr>
<td>2000 - 2999</td>
<td>25,000 - 74,999</td>
</tr>
<tr>
<td>&lt; 2000</td>
<td>&lt; 25,000</td>
</tr>
</tbody>
</table>

When CeeNU is used in combination with myelosuppressive drugs, the doses should be adjusted accordingly.
PHARMACEUTICAL INFORMATION

Chemistry:

\[
\begin{align*}
\text{O} & \quad \text{NH} \\
\text{N-CH}_2\text{-CH}_2\text{-Cl} & \quad \text{N=O}
\end{align*}
\]

Trade Name: CeeNU
Proper Name: Lomustine
Chemical Name: 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea
Molecular Formula: \( \text{C}_9\text{H}_{16}\text{ClN}_3\text{O}_2 \)
Molecular Weight: 233.71
Description: Yellow powder. Soluble in 10% ethanol (0.05 mg/mL) and in absolute alcohol (70 mg per mL). It is relatively insoluble in water (<0.05 mg/mL). It is relatively un-ionized at a physiological pH.

STABILITY

Unopened bottles of CeeNU (lomustine-CCNU) capsules are stable for 36 months at room temperature.
Storage: PROTECT FROM LIGHT. Avoid excessive heat (over 40°C).

AVAILABILITY

The capsules of CeeNU (lomustine-CCNU) are prepared in three dosage strengths: 10 mg, 40 mg, and 100 mg.

All capsules contain mannitol and magnesium stearate as inert ingredients.
CeeNu capsules are available as follows:
- 10 mg in bottles of 20 capsules
- 40 mg in bottles of 20 capsules
- 100 mg in bottles of 20 capsules
SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

1. Only the appropriate number of CeeNU (lomustine-CCNU) capsules required for a single administration should be dispensed. Patients should be told that CeeNU is taken as a single oral dose and will not be repeated for at least 6 weeks.

2. Preparation of CeeNU should be done in a vertical laminar flow hood (Biological Safety Cabinet - class II)

3. CeeNU capsules should not be placed in automated counting machines. The counting and pouring of CeeNU should be done carefully and the equipment used should be rinsed with water and then thoroughly cleaned with detergent and water.

4. Personnel handling CeeNU should wear gloves, safety glasses, a mask and disposable protective clothing.

5. Vials and other materials which have come in contact with CeeNU should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

6. Personnel regularly involved in the preparation and handling of CeeNU should have bi-annual blood examinations.
Kline et al. used a biological procedure for the determination of drug levels of CeeNU (lomustine-CCNU). The biological target was L1210 leukemia. A dose response curve was determined for the drug when given simultaneously with the inoculation of a designated number of leukemia cells, using % of cures and median survival time as the parameters of response. The drug was also administered at a series of time intervals prior to the inoculation of leukemia cells and the dose level equivalence at the time of leukemic inoculation was estimated by reference of the observed therapeutic response to that obtained for the standard curve. The curve for percentage retention of administered CeeNU had a shallow slope and the half-life of the drug in the host was estimated to be 94 minutes.

Oliverio et al. studied the metabolic fate of CeeNU using the 14C label in each of three positions of the molecule; the ethyl, carbonyl, and cyclohexyl moieties. In rodents, 24 hours after intraperitoneal or oral dose of the ethyl or cyclohexyl labelled CeeNU, 75% of the radioactivity appeared in the urine, while about 10-20% of carbonyl or ethyl labelled CeeNU was expired as 14CO2. In dogs and monkeys, CeeNU was also rapidly degraded and excretion of 14C was primarily in the urine. Plasma levels of 14C fell off rapidly in the first hour followed by a slower disappearance. After an intravenous injection, the CSF/plasma ratio of ethyl labelled CeeNU was three, while that for the cyclohexyl-labelled moiety was unity. This agrees with the observation that the cyclohexyl portion of the molecule is 60% plasma protein bound while the ethyl portion is not bound. The results support the suggested intermediate formation of an isocyanate moiety during the degradation of nitrosoureas in vivo. The identified metabolites and cyclohexylisocyanate were inactive against L-1210.

Studies conducted to determine the effects of NSC 79037 in polyethoxylated vegetable oil and normal saline (ratio of 1:9) applied topically to the hamster cheek pouch revealed no thromboembolism as concentrations 2.5 mg/ml. The only effect produced with this concentration was a slight decrease in the rate of venule and arteriole blood flow in 1/6 hamsters and a slight to moderate decrease in the venule flow of a second animal. Administration of a concentration at 0.625 mg/ml or the vehicle alone produced no detectable effect.

No thromboembolism was observed in the hamster cheek pouch microcirculation after single intrajugular injections of CeeNU in polyethoxylated vegetable oil and normal saline at doses ranging from 0.3125 to
20.0 mg/kg. However, a dosage of 0.625, 1.25, 2.5, 5.0, 10.0 or 20.0 mg/kg produced a decrease in cheek pouch venule blood flow varying from slight to moderate-severe. A slight to moderate-severe decrease in blood flow was also noted in the arterioles at drug levels ranging from 1.25 to 20 mg/kg with some vasoconstriction recorded at the 3 highest levels. At 20.0 mg/kg WBC stickiness was reported only once. The "no effect" level appeared to be 0.3125 mg/kg. Injection of the vehicle alone at volumes equivalent to those employed with 2.5, 5.0, 10.0, and 20.0 mg/kg drug dosages produced some vasoconstriction and a decrease in the rate of arteriole and venule blood flow. Microcirculation appeared normal when the vehicle alone was injected at a volume equivalent to that of a 1.25 mg/kg drug dosage. A mean recovery time of 17 minutes (5-35) was required for normal flow after intravenous injection in hamsters treated with the drug, compared to a mean recovery period of 6 minutes (2-10) in those receiving only the polyethoxylated vegetable oil and saline vehicle. It was concluded that cardiovascular effects observed were, in part, due to the vehicle employed.

Comparison of mortality levels in mice and rats for single oral doses of BiCNU and CeeNU on a mg/kg, mg/m², or mmole/kg basis revealed that BiCNU was twice as toxic as CeeNU.
The toxicity of CeeNU (lomustine-CCNU) was investigated primarily by the Mason Research Institute under contract with the National Cancer Institute. The parenteral toxicity of CeeNU may be summarized as follows:

a) Single Dose (IV infusion):

Dog: Maximum tolerated dose (MTD) - 0.625 mg/kg  
Primary toxicity = Depressed hematopoiesis, lymphoid tissue.  
Secondary toxicity - Delayed hepatotoxicity  
Rhesus Monkey: MTD = 1.25 mg/kg  
Primary toxicity = nephrotoxicity  
Secondary toxicity - Depressed hematopoiesis, hepatotoxicity.

b) Multiple Dose (IV infusion):

Dog: 2 or 3 doses of 1.25 mg/kg given at weekly intervals = cumulative hepatotoxicity.

The toxicity of CeeNU given orally may be summarized as follows:

a) Single Dose (capsules)

Dog: MTD = 2.0 mg/kg

b) Multiple Dose (capsules - dog, gavage - monkey)

Dog: MTD - 0.65 mg/kg/day x 14  
Rhesus Monkey: MTD = 0.15 mg/kg/day x 14

c) Delayed Hepatotoxicity (capsules)

Dog: A single oral dose of 4 mg/kg produced hepatotoxicity that persisted for 2-3 months after drug treatment.
REFERENCES

1. Hansen, H., Selawry, O., Muggia, F.M. and Walker, M.D.
   Clinical studies with 1(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC 79037)

2. Israel, L. and Chahinian, P.
   Comparative Toxicity on Leukocyte and Platelet of Two Regimens of CCNU.

   Analysis of Growth Curve Modifications in 30 Measurable Tumors, Under the Influence of 75
   mg/M2 of CCNU Every 3 Weeks.

4. Protocol ALB #7282. Methyl-CCNU and CCNU in the Treatment of Advanced Malignant Solid
   Tumors of Adults.


6. WCG 809. CCNU (NSC-79037) Given Orally for the Treatment of Lymphoma and other
   Neoplasma. A Phase II Study.

   CCNU (1-[2-chloroethyl]-3-cyclohexyl-1-nitrosourea, NSC-79037) in the Treatment of Cancer.

7A. Hoogstraten, B., and Luce, J.
   CCNU (1-[2-chloroethyl]-3-cyclohexyl-1-nitrosourea) and Bleomycin in the Treatment of Solid
   Tumors and Lymphoma.

8. DeConti, R., Hubbard, S., Pinch, P. and Bertino, J.
   Treatment of Advanced Neoplastic Disease with 1-[2-chloroethyl]-3-cyclohexyl-1-nitrosourea
   (CCNU; NSC-79037).

9. Broder, L. and Hansen, H.
   1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, NSC-79037): A Comparison of Drug
   Administration at Four-week and Six-week Intervals.

10. Perloff, M., Muggia, F., and Ackerman, C.
    Role of a Nitrosourea (Lomustine) in Advanced Non-hematologic Cancer: Clinical Experience and
11. Bertolone, S., Holton, C., Pratt, C. and Short, B.
Response of Advanced Childhood Malignancy to 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU).
Western Pediatric Hematology Abstract.

12. Fewer, D., Wilson, C., Boldrey, E. and Enot, J.
Phase II Study of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU; NSC-79037) in the Treatment of Brain Tumors.

12A. Rosenblum, M., Reynolds, A., Smith, K., Rumack, B. and Walker, M.
Chloroethyl-cyclohexyl-nitrosourea (CCNU) in the Treatment of Malignant Brain Tumors.

13. Hansen, H., and Muggia, F.
Treatment of Malignant Brain Tumors with Nitrosoureas (Letter).

Superiority of Adriamycin over Oral Nitrosoureas in Patients with Breast Cancer. Report on SWG-449
Southwest Cancer Chemotherapy Study Group.

15. Krakoff, I.

16. Ahmann, D., Bisel, H. and Hahn, R.
Difficulties Designing Clinical Trials as Exemplified by a Phase 2 Drug Evaluation of 5[3,3-Bis(2-chloroethyl)-1-triazenol]-indazole-4-carboxamide and 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea in Patients with Disseminated Breast Cancer.

17. Cunningham, T.J., Rosner, D., Olson, K.B., Nemoto, T., Dao, T., and Horton, J.
A Comparison of 5 Azacytidine (5AC) with CCNU in Breast Cancer.

Eastern Cooperative Oncology Group Report.

19. Moertel, C.

20. Moertel, C., Schutt, A., Reitemeier, R and Hahn, R.
Sequential 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC 79037) and 5-Fluorouracil (NSC 19893) Therapy of Gastrointestinal Cancer.
20A. Moertel, C., Schutt, A., Reitemeier, R. and Hahn, R.
A Phase II Study of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC 79037) in the Palliative Management of Advanced Gastrointestinal Cancer. 

21. Moertel, C., Reitemeier, R., Schutt, A., and Hahn, R.
Effect of Resection of the Primary Neoplasm on Responsiveness to Chemotherapy of Patients with Large Bowel Cancer.

22. Klassen, D. and Rapp, E.


24. Selawry, O., and Hansen, H.

25. Takita, H. and Brugarolas, A.
Effect of CCNU (NSC-70837) on Bronchogenic Carcinoma. 

26. Carr, D.
Lung Cancer. CCNU/Methyl CCNU. 


28. Ahmann, D., Hahn, R. and Bisel, H.
A Comparative Study of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC 79037) and Imidazole Carboxamide (NSC 45388) with vincristine (NSC 67574) in the Palliation of Disseminated Malignant Melanoma. 

29. WCG 119. CCNU versus CCNU + Vincristine for Treatment of Disseminated Malignant Melanoma. Phase III - Randomized. 
Western Cancer Group Report.

30. Mittelman, A., David, A., and Murphy, G.
Lomustine Treatment of Metastatic Renal Cell Carcinoma. 
31. Mittelman, A., and Murphy, G.
Treatment of Metastatic Renal Cell Carcinoma with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU).

32. Costanza, M.
Eastern Cooperative Oncology Group Report.

33. Einhorn, L., Livingston, R. and Gottlieb, J.
Combination Chemotherapy with Adriamycin (NSC 123,127) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, NSC 79037).

34. Wallace, H.J., Hoagland, H., Ellison, R., Glidewell, O., and Holland, J.
CCNU Plus Cytosine Arabinoside (ARA-C) Treatment of Acute Myelocytic Leukemia Compared with Thioguanine (TG) Plus ARA-C. Abstract 400

Acute Leukemia Group B Report.


38. ALB 7251. A Study of 4 Drug Combination Chemotherapy of Stage III and IV Hodgkin's Disease.
Acute Leukemia Group B Report.

39. WCG-120. COP versus CCNU-OP in Non-Hodgkin's Lymphoma.
Western Cooperative Group Report.

40. Magrath, I. and Ziegler, J.

41. Ziegler, J.

42. Carter, R. and Kremetz, E.
Combination Treatment of Metastatic Malignant Melanoma with Urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), Vincristine (VCR) and Dimethyltriazeno Imidazole Carboxamide (DIC). Abstract 351

43. COG 7130. DTIC and Combination Therapies for Metastatic Melanoma. Phase III. Central Oncology Group Report.
44. Gerner, R.
Unpublished Report from Roswell Park Memorial Institute.


The Cyclic Use of CCNU, Cytoxan and Alkeran Plus Prednisone in Patients with Multiple Myeloma.

47. Lindell, T., Moseley, H., and Fletcher, W.
Combination CCNU-Bleomycin Therapy for Squamous Cell Carcinoma.
Central Oncology Group Report.

48. Fletcher, W.
4-Drug Combination Therapy for Squamous Cell Carcinoma Using CCNU, Methotrexate, Velban and Bleomycin.
Central Oncology Group Report.

49. Little, Arthur, D. Inc.
Effects of CCNU (NSC 79037) in polyethoxylated vegetable oil and normal saline on the microcirculation of the hamster cheek pouch after topical application and intravenous injection.

Duration of Drug Levels in Mice as indicated by residual antileukemic efficacy Chemotherapy 13: 28-41, (1968).

51. Oliverio, Vincent, T. et al.
The absorption, distribution, excretion and biotransformation of the carcinostatic 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea in animals.

52. Thompson, George, R. and Larson, Robert E.
A Toxicologic comparison of the potency and activity of 1,3-Bis (2-chloroethyl) - 1-nitrosourea (BCNU) and 1-(2-Chloroethyl)-nitrosourea (CCNU) in mice and rats. Toxicology and applied Pharmacology Vol. 21: 405-413, (1972).

53. Dent, R.G.
Fatal pulmonary toxic effects of lomustine.

54. Vats, Tribhawan, S. and Langston, Claire M.
Pulmonary fibrosis associated with lomustine (CCNU): A Case Report.

56. Cruz, A.B., Metter, G., Armstrong, D.M., Aust, J.B., Fletcher, W.S., Wilson, W.L., and Richardson, J.D.
   Treatment of Advanced Malignancy with CCNU (NSC 79037).  A Phase II Cooperative Study with Long-Term Follow-up.

57. Silver, H.K.B. and Morton, D.L.

58. ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs.

59. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs.

60. O'Driscoll, B.R. et al.
   Active Lung Fibrosis Up to 17 Years After Chemotherapy With Carmustine (BCNU) In Childhood.