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Nitrosoureas: A reappraisal of clinical trials

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THE NITROSOUREAS (BCNU, CCNU, methyl CCNU) represent a new class of antineoplastic agents with a broad spectrum of antitumor activity. They are cell-cycle nonspecific cytotoxic agents. Postulated modes of action and pharmacology of these nitrosoureas are reviewed. Their therapeutic effectiveness as single agents and in combinations have been recognized in malignant lymphomas, multiple myeloma, melanoma, glioblastoma multiforme, gastric and colorectal carcinoma, and small-cell carcinoma of the lung. The nitrosoureas are administered on an intermittent 6–8-week schedule because of delayed and frequently severe bone marrow toxicity which may be cumulative in nature.

The nitrosoureas are a group of cell-cycle nonspecific antineoplastic agents which have a broad spectrum of activity against a number of animal tumor systems and against human hematologic malignancies and solid tumors.[1,2] They are synergistic in combination chemotherapeutic regimens, have the ability to cross the blood–brain barrier when administered systemically, and may be administered as single doses at approximately 6-week intervals. Two nitrosoureas, 1,3-*bis*(2-chloroethyl)-1-nitrosourea (BCNU, Carmustine®) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, Lomustine®), have recently become commercially available. A third nitrosourea, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (methyl CCNU, MeCCNU, Semustine®), remains investigational. We have reviewed the published data on these three nitrosoureas to define and highlight their present and potential future roles in combination chemotherapy and to focus upon their spectrum of action and unpredictable hematologic toxicity. A fourth nitrosourea, streptozotocin, has recently been reviewed in detail and will not be discussed here.[3,4]

Preclinical studies

In 1959 Greene and Greenberg noted that 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) was effective in prolonging the life span of mice receiving intraperitoneal implants of L1210 leukemia.[5] This discovery led to a systemic search of compounds structurally related to MNNG. It was observed that 1-methyl-1-nitrosourea (MNU) was more effective than MNNG in increasing the host life span of mice injected intraperitoneally or subcutaneously with L1210.[6] MNU was also effective against intracerebrally implanted L1210

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leukemia. Subsequent deliberate synthesis of other 1-methyl-1-nitrosurea derivatives revealed that 1-(2-*bis*(2-chloroethyl)-1-nitrosourea (BCNU) had curative potential in the BDF_1 mouse implanted with as many as 10^7 L1210 cells intraperitoneally or 10^5 L1210 cells intracerebrally.[7]

The nitrosourea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), produced more "cures" than BCNU in the experimental treatment of mice with L1210 and was active in the Walker carcinosarcoma 256 and melanoma B16 tumor systems.[1] CCNU, when used in combination with cytosine arabinoside, was curative in mice receiving intravenous implants of 10^7 L1210 cells even when the initiation of treatment was delayed until 24 hours before the median day of death.[8]

1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (methyl CCNU) was superior to BCNU and CCNU in the treatment of mice implanted with Lewis lung carcinoma. As a surgical adjuvant, in combination with cyclophosphamide, methyl CCNU cured a significant proportion of BDF_1 mice that received subcutaneous implants of Lewis lung tumor even when they were treated at a time when lung metastases had occurred. These tumors were not curable at that time with any of the standard alkylating agents, antimetabolites, vinca alkaloids, dactinomycin, cytosine arabinoside, or hydroxyurea.[1,9] Methyl CCNU also possessed superior activity against the relatively unresponsive B16 malignant melanoma and C3H breast carcinoma.[1]

Mechanism of antitumor action

The nitrosoureas (Fig. 1) are cell cycle nonspecific agents.[10] However, there is a somewhat greater degree of cell kill in the M phase and G_1/S phase boundary of the cell cycle. Alkylation and carbamylation have been suggested as the potential modes of action of the nitrosoureas, but the precise mechanism is unclear.[7,11-15]

BCNU inhibits DNA synthesis of Ehrlich ascites tumor cells *in vitro*[16] and L1210 leukemia *in vivo*.[14,17,18] Under experimental conditions, BCNU is able to inhibit the incorporation of ^{14}C-formate into purines of DNA and RNA but greater inhibition of nucleic acid than of protein synthesis occurs. It has been suggested that BCNU interferes with the *de novo* synthesis of purine ribonucleotides and with the conversion of purine nucleotides to DNA

BCNU AND OTHER NITROSOUREAS

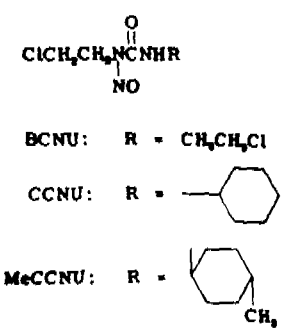

FIGURE 1. Structural formulas for the halogenated N-alkyl-N-nitrosoureas

bases.[1] In addition to its postulated role as an alkylating agent, BCNU interferes selectively with the utilization of histidine or its metabolites, as demonstrated *in vivo* in mice bearing L1210 ascites tumor cells and in human leukemic cells.[19] BCNU *in vitro* can inhibit formimino transferase, the enzyme which transfers the formimino group from formiminoglutamate to tetrahydrofolic acid.[1] This suggests that BCNU may interfere with one-carbon metabolism.

CCNU labeled with ^{14}C in the cyclohexyl moiety binds extensively to proteins in the L1210 mouse *in vivo*, to suspensions of L1210 cells *in vitro*, and to nucleic acids and proteins *in vitro*. CCNU labeled with ^{14}C in the ethylene moiety binds to both nucleic acids and proteins but with far less avidity than CCNU labeled in the cyclohexyl moiety. These data suggest that CCNU modifies nucleic acids by alkylation and proteins by cyclohexyl carbamylation.[11,12]

Pharmacology

All three nitrosoureas are lipid soluble with methyl CCNU having the greatest lipid solubility and BCNU the least.[20] CCNU and methyl CCNU are asymmetric molecules which are more easily radiolabeled than BCNU and were, in part, developed to study the pharmacologic disposition of the nitrosoureas.

Disposition studies with ^{14}C-labeled nitrosoureas suggest that BCNU, CCNU, and methyl CCNU are rapidly absorbed from the gastrointestinal tract with peak plasma levels of degradation products appearing 1-6 hours after administration.[20] The

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Disposition Stud

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CCNU (given p.o.)
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^{14}C-Cyclohexyl m
^{14}C-Chloroethyl m
Methyl CCNU (given
^{14}C-Cyclohexyl m
^{14}C-Chloroethyl r

...sma levels of these degradation products are ...longed and the urinary excretion is moderately ...w (Table 1)

Radiolabeled BCNU has a half-life of 34 hours ...hen given orally and 67 hours when given intravenously.[21] Sixty to 70% of the radiolabel from ...CNU is recovered in the urine by 96 hours with ...dually no fecal excretion.[21] CCNU is readily ...sorbed when given orally with peak plasma levels ...ched between 1 and 4 hours. No intact drug is ...tectable in plasma at any time following an oral ...se of CCNU. Urinary excretion of radiolabeled ...CNU varies between 56% and 77% of an orally ...ministered dose depending upon the location of ...e radiolabel.[22] Methyl CCNU undergoes prompt ...tal absorption with no intact drug detectable ...bsequently in the plasma. Peak plasma levels ...cur between 3 and 6 hours. Approximately 60% ...radiolabeled methyl CCNU can be recovered in ...e urine by 48 hours.[22]

Prolonged plasma levels of radioactivity probably reflect a combination of plasma protein binding and active enterohepatic recirculation of the degradation products. The entry of the nitrosourea degradation products into the cerebrospinal fluid (CSF) is prompt (within 30–60 minutes), closely parallels changes in the concurrent plasma levels of radioactivity, and may be related to the lipid solubility of the parent nitrosoureas. Absolute levels in the CSF of man are 15–30% of the simultaneous plasma levels. BCNU, CCNU, and methyl CCNU cannot be detected as the intact parent compounds in the CSF.[21,22]

TABLE 1

Disposition Studies with ^{14}C-labeled Nitrosoureas in Man

Location of Radiolabel	Time to Peak Plasma Level (hours)	Plasma Half-life (hours)
...NU (given p.o.)	1	34
...given I.V.)	3	67
...CNU (given p.o.)		
^{14}C-Carbonyl moiety	1	5 (first phase)
		>27 (second phase)
^{14}C-Cyclohexyl moiety	3	5 (first phase)
		>27 (second phase)
^{14}C-Chloroethyl moiety	4	22
...ethyl CCNU (given p.o.)		
^{14}C-Cyclohexyl moiety	3	24 (first phase)
		72 (second phase)
^{14}C-Chloroethyl moiety	6	36

The parent nitrosoureas do not appear to be the active antineoplastic agents themselves because they cannot be recovered from plasma, urine or cerebrospinal fluid after administration.[21,22] A number of degradation products have been postulated as the potentially active compounds.[23–25] These have included 2-chloroethyl isocyanate and 2-chloroethylamine for BCNU and cyclohexyl isocyanate and cyclohexylamine for CCNU. The hepatic microsomal drug-metabolizing system is involved in nitrosourea degradation.

Drug toxicity and dosage scheduling

The clinical use of nitrosoureas as single agents or in multidrug combination regimens has been based on the intermittent single-dose schedule and the broad spectrum of antitumor activity.

As single agents in patients with good bone marrow reserve and limited prior chemotherapy and or radiotherapy, BCNU is administered intravenously in a dose of 220–225 mg/m^2 every 6–8 weeks (or 80 mg/m^2 intravenously daily ×3 every 6–8 weeks), CCNU is given orally in a dose of 100–130 mg/m^2 every 6–8 weeks, and methyl CCNU is given orally in a dose of 200–225 mg/m^2 every 6–8 weeks.[26] The intermittent dosage schedule was developed because of delayed marrow toxicity. Advocates of BCNU fractionation argue for somewhat less gastrointestinal toxicity. Qualitatively, it is difficult to discern major toxicity differences among these three nitrosoureas.

Delayed and profound bone marrow toxicity is the most serious side effect of the nitrosoureas. The typical (late) nadir is seen in all patients, usually occurring between weeks 3 and 5 for platelets and weeks 4 and 7 for granulocytes and lasting between 1 and 2 weeks. This delayed nadir is an advantage when using the nitrosoureas in combination with other agents that typically have an earlier myelosuppressive action since the nadirs are not superimposed. An early granulocyte and platelet nadir may be seen in one fourth to one-third of the patients, occurring 10–14 days after the administration of the nitrosourea and lasting 4–10 days[27] as demonstrated in Figure 2. The early nadir predicts a more severe late nadir. Approximately 1–2% of

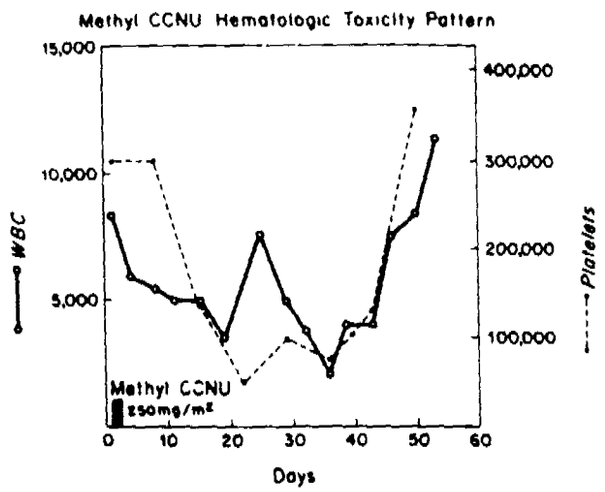

FIGURE 2. Hematologic toxicity pattern of methyl CCNU with double nadir of leukopenia [27]

previously untreated patients on their first exposure to a nitrosourea will experience life-threatening peripheral pancytopenia in association with marked marrow hypoplasia. The basis for this idiosyncratic reaction is not understood.

Cumulative marrow effects are manifested by lower nadirs at a given dose level, earlier appearance of nadirs, longer duration of marrow suppression, and average nadirs at a lower level [26]. A progressive anemia may be noted after each course with failure of the hemoglobin level to rise back to its baseline. This refractory anemia may be minimized by spacing nitrosourea courses further apart (8 weeks rather than 6 weeks) and may require red blood cell transfusions. It is essential that complete blood counts be checked at least once a week during nitrosourea therapy, possibly twice a week in that subgroup of patients which manifests both early and late nadirs. In combination with other drugs or radiotherapy, the dosage of nitrosourea should be reduced.

Gastrointestinal toxicity consists of nausea and vomiting 2–6 hours after administration and persists for up to 24 hours. It may be somewhat ameliorated by antiemetics and fasting. This toxicity is not cumulative and appears to be centrally mediated so that it does not interfere with the absorption of the oral nitrosoureas [26–28].

Less frequent side effects include alopecia, stomatitis, diarrhea, anorexia, reversible abnormalities of liver chemistries, hyperesthesia, dizziness, and gynecomastia [28, 29]. BCNU may cause conjunctival flushing. A local phlebitis with burning and hyperemia at the site of injection has been noted with BCNU [29, 30]. Endophlebitis associated with each course of BCNU may cause permanent loss of veins at administration sites.

Of recent concern is the pulmonary toxicity of BCNU (and probably methyl CCNU), not surprising, however, because the potential for producing fibrosis of the lung was noted in dogs during the initial development of BCNU [32–38]. Clinical symptoms usually include progressive dyspnea and chronic nonproductive cough, while chest x-rays reveal interstitial infiltrates which may be patchy or diffuse. Pathologic examination of the lung reveals a nonspecific pulmonary fibrosis and alveolar cell dysplasia postulated to be secondary to the alkylating action of nitrosoureas on respiratory epithelium. Prior to the development of lung toxicity, patients have generally received 1–4 g of drug over 6 months to 4 years. The clinical outcome is variable with recovery in some patients and progressive respiratory failure in others. The role of corticosteroids in ameliorating the pulmonary insufficiency induced by nitrosoureas is unclear.

Nitrosoureas have been incriminated in the development of chronic renal failure and interstitial nephritis [29–31]. Azotemia is generally delayed and not associated with hypertension, proteinuria, or other urinary sediment abnormalities. Kidney size is decreased while pathologic examination often discloses glomerulosclerosis, severe tubular loss, wrinkling of the glomerular basement membrane,

some degree of medullary interstitial fibrosis.[40] The mechanism of nitrosourea-induced renal failure is not known although renal toxicity was seen in preclinical trials in animals.[20]

Two cases of acute nonlymphocytic leukemia have been reported in patients treated with long-term nitrosourea therapy for brain malignancies. One patient received BCNU and CCNU; the other patient received methyl CCNU.[42] Whether this represents a coincidental finding or not is unclear at present.

Antineoplastic activity by tumor types

Several comprehensive reviews have been published concerning the effectiveness and clinical trials of BCNU,[1] CCNU,[3] and methyl CCNU.[41] It is important to recognize that nitrosoureas are *not* necessarily interchangeable compounds and that substitution of one nitrosourea for another may be inappropriate in the management of an individual tumor.

Response rates for nitrosoureas alone or in combination as used in this review are defined as follows: Complete response (CR) means complete disappearance for all clinically measurable malignant disease without the development of new malignant lesions lasting for at least 4 weeks. Patients with bony metastases must have normalization of all bone x-rays. Partial response (PR) means greater than or equal to 50% decrease in the product of the two greatest perpendiculars of a tumor mass lasting for at least 4 weeks without the increase of any area of known malignant disease or the appearance of new areas of malignant disease. For liver metastases, a partial response refers to a 50% or greater decrease in the sum of the liver edge measurements taken below the right and left costal margins in the respective mid clavicular lines, and below the tip of the xyphoid. Objective response refers to the sum of complete and partial responses. Table 2 reviews the published response rates to the three different nitrosoureas in a variety of neoplasms. We will review the common tumor sites where the nitrosoureas have been adequately evaluated.

Gastrointestinal carcinoma

Gastric carcinoma

The median survival for gastric adenocarcinoma is 4-6 months from the time of documentation of incurability. Only 12% of patients are alive at 1 year.[9] Although 5-fluorouracil (5-FU) has been considered the "standard" agent for treating advanced gastric adenocarcinoma, objective response rates are only 15-20% and are short-lived. There is no significant difference in survival in a large group of patients treated with 5-fluorouracil as compared to an untreated group although responders live longer.[46,52] Both BCNU and methyl CCNU are active agents in gastric carcinoma with objective response rates of 18% and 13%, respectively, and median durations of response of 4 months.[45] CCNU has no activity in gastric carci-

TABLE 2

Objective Response Rates to Single-Agent Nitrosurea Chemotherapy

Tumor Type	Refs	BCNU		CCNU		Methyl CCNU	
		No. of Evaluable Patients	No. of Responses[a] (%)	No. of Evaluable Patients	No. of Responses (%)	No. of Evaluable Patients	No. of Responses (%)
[illegible]nic	45	33	6 18	11	0 0	15	2 13
[illegible]oma	45	31	0 0	4	2	15	2 13
[illegible]rectal	43, 44, 46	69	7 10	199	14 7	168	18 11
[illegible]ast	43, 44, 47	76	16 21	170	20 12	100	4 4
[illegible]noma	48	122	22 18	133	17 13	108	18 17
[illegible] all histologies	49	83	9 11	279	46 16	341	33 10
[illegible]nant Glioma	43, 44, 50	69	32 46	73	27 37	27	6 22
[illegible]kin's	1, 43, 44	213	94 44	84	40 48	74	19 26
Non-Hodgkin's lymphoma	1, 43, 44	107	30 28	52	13 25	57	10 18

[a] Responses = complete plus partial responses as defined in the text.

TABLE 3

Prospective Randomized Studies of 5-Fluorouracil-Nitrosourea Combinations in Patients with Metastatic Gastric Cancer

	Refs	No. of Evaluable Patients	No. of Responses	Percentage	Median Survival Duration from the Onset of Chemotherapy (months)
5-FU	47	28	8	29	7.4
BCNU	47	23	4	17	3.5
5-FU + BCNU	47	34	14	41	7.7
Methyl CCNU	48	37	2	6	3.0
5-FU + methyl CCNU	48	30	12	40	5.0

noma. As single agents BCNU and methyl CCNU have a minimal impact on survival. At the Mayo Clinic 5-fluorouracil and BCNU when used in combination produced a higher response rate (41%) as compared to 5-FU alone (29%) or BCNU alone (17%) in patients with advanced gastric carcinoma and measurable metastatic lesions. Median survival was 3.5 months for BCNU, 7.4 months for 5-FU, and 7.7 months for the combination (Table 3). However, the combination of 5-FU and BCNU was superior to 5-FU at a statistically significant level only at 18 months from the start of therapy with 26% of the patients receiving the combination alive compared to 7% with 5-fluorouracil alone.[56]

The Eastern Cooperative Oncology Group (ECOG) compared 5-FU and methyl CCNU combination chemotherapy versus methyl CCNU alone in patients with advanced measurable gastric cancer and demonstrated a statistically significant survival improvement and response rate for the combination.[54] In patients with nonmeasurable metastatic gastric carcinoma, 5-FU alone and 5-FU plus methyl CCNU produced equivalent survival rates of 6.5 months from the onset of therapy in a recently reported ECOG study.[55] It should be emphasized that the effectiveness of 5-FU-nitrosourea therapy has been demonstrated only for that select population of gastric cancer patients who have advanced measurable metastatic disease.

Both the Gastrointestinal Tumor Study

TABLE 4

Prospective Randomized Studies of 5-Fluorouracil-Nitrosourea Combinations in Patients with Advanced Large Bowel Cancer

Institution (Refs.)	Chemotherapy[a]	No. of Evaluable Patients	No. of Responses	Percentage	Median Survival Duration of All Patients from Onset of Chemotherapy (months)	
Mayo Clinic (63)	5-FU	41	8	19	–	No difference
	5-FU + MeCCNU + VCR	39	17	43	–	
Univ. Pretoria (64)	5-FU	45	10	22	6.5	
	5-FU + MeCCNU + VCR	46	17	37	7.8	
SWOG (65)	5-FU	42	4	9	–	No difference
	5-FU + MeCCNU	152	48	32	–	
ECOG (67)	5-FU + MeCCNU	88	9	10	6.0	
	5-FU + MeCCNU + VCR	81	10	12	7.3	
	5-FU + MeCCNU + DTIC	83	14	14	9.1	
	5-FU + MeCCNU + VCR + DTIC	71	11	15	9.0	
	5-FU + hydroxyurea	73	15	21	7.3	
Mayo Clinic (68)	5-FU + MeCCNU	33	7	21		No difference
	5-FU + MeCCNU + MER-BCG	29	3	10		
	5-FU + MeCCNU + VCR	31	6	19		
	5-FU + MeCCNU + VCR + MER-BCG	32	9	28	–	

[a] MeCCNU = methyl CCNU; 5-FU = 5-fluorouracil; DTIC = dimethyltriazenoimidazole carboxamide; MER-BCG = methanol extraction residue of BCG.

Group[56,57] (GITSG) and the Southwest Oncology Group[58] (SWOG) are currently studying 5-FU methyl CCNU drug-containing regimens in patients with metastatic gastric carcinoma to better determine the effects on patient survival. Also ongoing is a GITSG adjuvant study comparing 5-FU-methyl CCNU combination therapy to no additional therapy in a group of patients undergoing curative surgery for gastric cancer.

Colorectal carcinoma

Patients with carcinoma of the colon have a median survival of 7.0 months from the time of proof of measurability.[59] The objective response rate to single-agent 5-FU in advanced colorectal cancer is 15-20% with a modest improvement in survival in the small group of responders.[60] The nitrosoureas appear to have limited therapeutic activity when used alone with objective response rates of 10% for BCNU, 7% for CCNU, and 11% for methyl CCNU.[61-63,66] Objective response rates to methyl CCNU are higher in previously untreated patients with colorectal carcinoma than in previous treated patients (21% versus 4% respectively).[59,62]

Despite four initial studies reporting augmented response rates with 5-FU + methyl CCNU combination chemotherapy[63-66] over 5-FU alone, several subsequent studies have been unable to confirm the increased response rate.[67-70] Those studies which were prospective and randomized are summarized in Table 4. The two Mayo Clinic studies are of interest because of the failure of one to support the findings of the other. Methyl CCNU in combination with 5-FU alone or with the addition of vincristine and/or immunotherapy (MER-BCG) did not improve response rates.[68] SWOG comparing 5-FU plus methyl CCNU to 5-FU plus mitomycin C observed response rates of 16% versus 18%.[69] Although the 5-FU was given by intravenous infusion, the response rate to 5-FU plus methyl CCNU was half of what the initial SWOG study[65] demonstrated. In a single-arm study by the Sidney Farber Cancer Institute,[70] 5-FU plus methyl CCNU produced a 4% response rate in 52 patients, far below that of the other studies. Other single-arm

TABLE 5

Prospective Single Regimen Studies of 5-Fluorouracil-Nitrosourea Combinations in Patients with Advanced Large Bowel Cancer

Institution (Refs.)	Chemotherapy[a]	No. of Evaluable Patients	No. of Responses	Percentage	Median Survival Duration of all Patients from Onset of Chemotherapy (months)	
Sidney Farber Cancer Inst. (70)	5-FU + MeCCNU	52	2	4	9.0	
Massachusetts General Hosp. (71)	5-FU + MeCCNU	22	2	9	—	
Geisinger Medical Ctr. (72)	5-FU + MeCCNU	36	6	16		
Georgetown Univ. (66)	5-FU + MeCCNU + VCR	25	10	40	8.0	
Memorial Sloan Kettering (73)	5-FU + MeCCNU (single dose) + VCR	32	3	9	—	No difference
	5-FU + MeCCNU (divided dose) + VCR	35	4	11	—	
Memorial-Sloan Kettering (74)	5-FU + MeCCNU + VCR + streptozotocin	54	15	27		
Vanderbilt Univ. (75)	5-FU + MeCCNU + VCR + mitomycin	19	2	11	4.5	
SWOG (76)	5-FU + MeCCNU + Baker's antifol	31	6	19		
CALGB (77)	5-FU + MeCCNU + daunomycin	27	5	19	—	

[a] See footnote to Table 4.

studies are summarized in Table 5, and also demonstrate low response rates for 5-FU–nitrosourea combination chemotherapy in patients with large bowel cancer.

The combination of 5-FU plus methyl CCNU should not be considered "standard" treatment for colorectal carcinoma patients because it has not been shown to reproducibly augment response rates, has never been demonstrated to increase median survival over 5-FU alone, and has caused greater toxicity than for single-agent 5-FU.

The GITSG in an on-going study is comparing the effect of adjuvant 5-FU plus methyl CCNU versus MER-BCG immunotherapy versus 5-FU plus methyl CCNU plus MER-BCG, to a no treatment control arm in patients with Dukes B_2 and C lesions following curative surgery.[78] With a median follow-up time of 13 months, there is no statistically significant difference in treatment arms with regard to time of recurrence or survival. Several other adjuvant prospective randomized trials incorporating methyl CCNU chemotherapy are underway in patients with colorectal carcinoma but results are not available as yet.[79]

Pancreatic carcinoma

The median survival from the time of documentation of operability of pancreatic adenocarcinoma is 3.5 months with only 8% of the patients alive at 1 year.[51] Fluorouracil produced a 15% objective response rate and 2.5-month median duration of response in patients with advanced pancreatic carcinoma.[80] In a prospective controlled study of patients with measurable disease, 5-FU was associated with a 16% objective response rate, BCNU with no responses, and the combination of 5-FU and BCNU with a 33% response rate.[52] The combination, however, was not significantly superior as compared to 5-FU alone either in terms of response rate or survival. In another prospective randomized study comparing 5-FU and BCNU with or without spironolactone, response rates for the two-drug versus the three-drug program were 16% versus 10% with overall median survivals of 3.4 and 4.6 months, not statistically different, and not better than the natural history of the disease.[80] Recent results from the ECOG in patients with nonmeasurable advanced pancreatic carcinoma revealed 3.5-month median survival for patients treated with 5-FU alone or in combination with methyl CCNU.[55] As single agents, BCNU, CCNU and methyl CCNU have little activity in pancreatic carcinoma and are not associated with improved survival.[45,49]

Other gastrointestinal carcinomas

CCNU has limited activity in the treatment of patients with squamous cell carcinoma of the esophagus and anus.[45] The other nitrosoureas have not been adequately evaluated in patients with these neoplasms. As single agents, nitrosoureas had no activity in hepatoma,[45] but the combination of 5-FU and BCNU has shown a 37% objective response rate in one series of 19 patients with hepatoma with three patients remaining in complete remission for greater than 3 years.[46]

Studies using nitrosoureas in patients with metastatic gastrointestinal neoplasms have demonstrated definite activity for these drugs. Since objective tumor responses are, in general, transient with nitrosoureas alone or in combination, nitrosoureas should not be considered "standard" therapy for this group of malignancies. However, it is evident that response rates are improved when nitrosoureas are combined with 5-fluorouracil. Adjuvant trials are thus underway to assess the effect of nitrosourea chemotherapy on disease-free survival and overall survival in high-risk patients undergoing curative surgery for gastric, colon, or rectal carcinoma. Such trials are based upon cell kinetic studies in animal models which show that the chance of eradicating a tumor is greatest when the tumor population is small.

Malignant melanoma

Nitrosoureas have limited but finite activity against malignant melanoma with cumulative objective response rates of 17–18% for BCNU, 11–13% for CCNU, and 15–17% for methyl CCNU.[48,81] As single agents BCNU and methyl CCNU compare favorably with the 23–24% cumulative objective response rate of imidazole carboxamide (DTIC) and each appears to be superior to CCNU.[48,81] Although nitrosoureas have been used in combination with DTIC, there is no evidence to show that these combinations are significantly superior to DTIC alone. ECOG has demonstrated overall objective response rates of 16% with DTIC alone, 17% with DTIC plus BCNU and

with DTIC plus methyl CCNU.[82] In an ongoing randomized prospective study, ECOG is comparing methyl CCNU in two different dosage schedules versus methyl CCNU + DTIC, plus hydroxyurea versus methyl CCNU plus BCG.[83] Initial response rates are 11–21% with no advantage for a triple drug arm or the methyl CCNU plus BCG arm over methyl CCNU alone. Similarly, the SWOG has demonstrated a 22–23% objective response rate with the combination of DTIC, BCNU, and vincristine with or without chlorpromazine in patients with advanced melanoma, not statistically different from that of DTIC alone.[84,85] Other SWOG studies have demonstrated response rates of 31% with DTIC, BCNU plus hydroxyurea[86,87] (HD); 30% with BHD plus vincristine[88] (BHDV); and 27% with BHD plus BCG.[86,87]

Melanoma patients who respond objectively to chemotherapy live significantly longer than nonresponders.[48,82] Nitrosoureas have their greatest activity against lymph node, subcutaneous, and skin metastases. However, despite the high lipid solubility and ability of nitrosoureas to cross the blood–brain barrier, there is no evidence demonstrating the effectiveness of nitrosoureas in either preventing or inducing the regression of central nervous system metastases.

Breast cancer

Cumulative reported objective response rates of breast cancer to single-agent nitrosourea therapy are 21% for BCNU,[47] 12% for CCNU,[37] and 4% for methyl CCNU.[38] Methyl CCNU is clearly an inactive agent in breast carcinoma. CCNU has been studied in combination with adriamycin in patients with advanced breast cancer refractory to hormonal manipulation and refractory to chemotherapy with cyclophosphamide, vincristine, methotrexate, 5-fluorouracil, and prednisone.[89-91] Objective response rates of 16–40% have been noted with the combination of CCNU plus adriamycin, but the rate and duration of response were very similar to that seen with adriamycin alone.[92] In a broad phase II study, the combination of adriamycin, BCNU, and cyclophosphamide produced a 50% objective response rate.[93] However, other adriamycin regimens give equivalent or better response rates.[94,95] The use of nitrosourea-containing combination therapy in previously untreated metastatic breast cancer needs to be explored further.

Lung cancer

Cumulative data suggests that the nitrosoureas have limited though definite activity in patients with lung cancer with overall response rates of 11% of BCNU, 16% for CCNU, and 10% for methyl CCNU.[39] When response rates are analyzed by the specific histology of the primary lung neoplasm, none of the nitrosoureas is clearly superior to any other nitrosourea.[43,44] Likewise, response rates for any single nitrosourea are equivalent among the four major histologic subtypes of lung cancer. The disappointingly low response rates have led to the incorporation of nitrosoureas into combination regimens.

The Veterans Administration Lung Group protocol # 4 compared cyclophosphamide alone to cyclophosphamide plus CCNU, to adriamycin plus CCNU, and to adriamycin plus cyclophosphamide in patients with advanced bronchogenic carcinoma using survival as an endpoint.[96] For patients with small cell carcinoma, large cell carcinoma, and adenocarcinoma of the lung, the four treatment arms appear similar in terms of both objective response rates and median survival.

ECOG has compared mechlorethamine (nitrogen mustard) alone to mechlorethamine and CCNU in a prospectively randomized trial of patients with advanced squamous cell carcinoma and large-cell carcinoma of the lung but was unable to demonstrate any differences in response rate or survival between the two arms.[97]

In a second prospective randomized study, ECOG compared cyclophosphamide alone to cyclophosphamide plus CCNU in patients with advanced small cell carcinoma and adenocarcinoma of the lung.[98] For patients with metastatic small-cell carcinoma objective response rates were 43% for cyclophosphamide plus CCNU compared to 22% for cyclophosphamide alone. However, a statistically significant survival advantage among responders could not be demonstrated for the two-drug combination. For patients with advanced adenocarcinoma of the lung, objective response rates were the same (12%) for both chemotherapy regimens as was the median survival for the subgroup of responders.

In a third prospective study, ECOG is comparing in patients with localized small-cell carcinoma radiation to the primary tumor and draining nodes alone versus radiation to the primary plus cyclo-

phosphamide and CCNU versus radiation to the primary and cranial irradiation versus all three modalities (lung and cranial irradiation plus chemotherapy).[89] Early results suggest a possible benefit for the radiotherapy arms in terms of preventing brain metastases but no difference as yet in overall antitumor responses.

Cyclophosphamide plus methotrexate has been compared prospectively to cyclophosphamide methotrexate, and CCNU in a National Cancer Institute VA Oncology Branch protocol.[100] For patients with adenocarcinoma, the three-drug arm was statistically superior to the two-drug arm with regard to objective response rate (38% versus 6%) and median survival (6.7 versus 4.0 months). For patients with small cell carcinoma, the three drug regimen produced a longer survival than for the two-drug regimen but this was not statistically significant. For both adenocarcinoma and small-cell carcinoma, responders in both arms lived longer than nonresponders. No treatment advantage could be shown for patients with squamous cell or large-cell undifferentiated carcinoma.

Of interest is the preliminary report by Pressant[101] who reported on a pilot study of amphotericin B and CCNU in bronchogenic cancer. Cells treated with amphotericin have enhanced uptake of ions as well as large and small molecules, and thus theoretically enables more drug to enter the cell. They treated 11 patients with amphotericin plus BCNU and documented five objective responses lasting 1.5–12+ months. These authors subsequently reported on a combination of amphotericin, adriamycin, BCNU and cyclophosphamide in patients previously resistant to the latter three drugs.[102] No responses were seen in three patients with lung cancer, but a complete remission was seen in one patient with acute myelomonocytic leukemia, one partial response was seen in multiple myeloma, and one partial response was noted in breast cancer.

The optimal role of nitrosoureas in the treatment of lung cancer remains to be defined, but the promising results in animal tumor models have not been confirmed in man. CCNU appears to increase response rates in small-cell carcinoma but has not consistently been shown to prolong survival. A number of uncontrolled studies which include a nitrosourea as part of a four- or five drug regimen have failed to identify the advantages of nitrosoureas in the treatment of patients with advanced lung cancer.[103–106]

Primary brain tumors

Malignant gliomas

Since the property of lipid solubility permits the nitrosoureas to cross the blood–brain barrier, these drugs have undergone numerous trials against primary central nervous system tumors (mostly astrocytomas and malignant gliomas).[107–109] Response rates of chemotherapy trials have been assessed in the literature by a decrease in tumor size as documented by brain scan (and more recently by computerized axial tomography) in conjunction with serial neurologic examinations. However, it is apparent that response rates to nitrosoureas are difficult to determine since many patients are receiving concomitant steroids and have received radiotherapy or undergone surgery in close temporal relationship to the use of a nitrosourea.[108]

Initial pioneering work at the University of California at San Francisco (UCSF) in patients with recurrent malignant gliomas demonstrated an impressive 51% (22/43) response rate for BCNU and 43% (10/23) response rate for CCNU in uncontrolled trials.[110,111] As reported, cumulative literature response rates are similar. BCNU 44–46%,[150] CCNU 37%,[43] methyl CCNU 22%.[4] Combination regimens have also been explored in uncontrolled trials at UCSF in the treatment of patients with recurrent malignant gliomas.[108,112] In responders and "probable" responders, response rates of 47% (21–45 patients) have been achieved with BCNU plus procarbazine, 41% (7–17) with BCNU plus vincristine, 31% (9–29) with BCNU plus 5-fluorouracil, and 60% (18–30) with CCNU plus vincristine plus procarbazine. Median durations of response in unequivocal responders have been 7–14, 7, and 9 months, respectively, but are not superior to BCNU alone (9 months) or CCNU alone (6 months). At the Roswell Park Memorial Institute, 26 of 50 nonirradiated patients with newly diagnosed gliomas placed on combination chemotherapy with methyl CCNU, procarbazine, and vincristine showed objective responses.[113] Thirteen patients remain in remission from 6 to 30+ months.

The Brain Tumor Study Group (BTSG) in a prospective randomized trial compared supportive therapy alone, BCNU alone, whole brain irradiation (5000–6000 rads) alone, and combined BCNU plus whole brain irradiation (5000–6000 rads) in

patients with malignant glioma following definitive surgical intervention using survival as the endpoint of the study[111] (Table 6). Two hundred twenty-two of 303 patients entered in the study satisfied the protocol requirements and were considered evaluable. When the adequately treated group was analyzed (that is, patients who received >5000 rads and one or two or more courses of BCNU) median survivals were 17.0 weeks for supportive care, 25.0 weeks for BCNU, 37.5 weeks for radiotherapy, and 40.5 weeks for BCNU plus radiotherapy. All three active treatment arms were superior to supportive care alone. Although the median survivals of the radiotherapy alone versus radiotherapy plus BCNU groups were not different, the 18-month survival of the radiotherapy plus BCNU group was statistically superior to the radiotherapy group. The results of the second and third BTSG trials are summarized in Table 6. A fourth study underway is comparing standard whole brain radiotherapy plus BCNU, whole brain radiotherapy plus streptozotocin, whole brain radiotherapy plus the radiosensitizer, misonidazole, followed by BCNU, and lastly superfractionation radiotherapy.

The ECOG/RTOG has reported preliminary results of a prospective trial which randomized patients with grade 3 and 4 gliomas following optimal surgical intervention to whole brain radiotherapy (6000 rads), whole brain radiotherapy plus a 1000-rad booster dose, whole brain radiotherapy plus BCNU, and whole brain radiotherapy plus methyl CCNU plus DTIC.[119] With short-term follow-up overall median survival is 38 weeks and is similar for the four treatment arms, but these results are preliminary.

Two additional randomized studies are summarized in Table 6 and fail to show an advantage for the addition of chemotherapy to surgery plus radiotherapy in terms of patient survival. Not shown in Table 6 is a recently reported cooperative

TABLE 6

Prospective Randomized Trials of Nitrosoureas in Combination with Surgery/Radiotherapy in the Treatment of Patients with Malignant Glioma

Reference	Treatment	No. of Evaluable Cases	Median Survival (weeks)
Brain Tumor Study Group[114]			
Surgery followed by	Supportive care only	222	17.0
	XRT*		37.5
	BCNU		25.0
	XRT + BCNU		40.5
Brain Tumor Study Group[115]			
Surgery followed by	XRT	332	36.0
	Methyl CCNU		31.0
	XRT + methyl CCNU		31.0
	XRT + BCNU		51.0
Brain Tumor Study Group[116]			
Surgery, followed by	XRT + procarbazine	326	Arms remain coded with median survival of 40–49 weeks
	XRT + methylprednisolone		
	XRT + BCNU		
	XRT + BCNU + methylprednisolone		
Mayo Clinic[117]			
Surgery, followed by	XRT	22	50.0
	CCNU	22	28.0
	XRT + CCNU	19	52.0
Mann[118]			
Surgery followed by	XRT	32	46.0
	XRT + BCNU	34	52.0
	XRT + CCNU	36	69.0

*XRT = cranial irradiation

European trial from the E O R T C Brain Tumor Group comparing glioma patients treated with surgery plus radiotherapy plus CCNU begun approximately 3 weeks following surgery ("early" CCNU) with a matched group in whom CCNU was begun only after tumor progression was noted ("late" CCNU).[120] The "early" CCNU group of 42 evaluable patients had a median survival from surgery of 45 weeks not statistically different from the "late" CCNU group of 39 evaluable patients which had a median survival of 62 weeks.

Currently it appears that in the management of patients with malignant gliomas, treatments that employ surgery plus cranial radiotherapy (with or without a nitrosourea) are superior to treatments that employ surgery plus a nitrosourea (without radiotherapy). Although nitrosoureas alone are clearly active in patients with recurrent glioma, their role in initial treatment as part of combined modality therapy remains unclear but hopefully will be elucidated through prospective trials that control both steroid and radiation doses. A higher proportion of 18-month survivors has been noted in patients receiving radiotherapy plus BCNU.

Medulloblastoma and ependymoma

The combination of CCNU plus vincristine plus procarbazine has been used in pilot studies for the treatment of postirradiation recurrent medulloblastoma with a 58% (7/12) response rate and 10-month median duration of response.[108,109] Severe myelotoxicity has been a major problem in this study probably because of the prior extensive cerebral and spinal axis irradiation.

The Children's Cancer Study Group (CCSG) is presently studying the efficacy of combined modality therapy in patients with medulloblastomas and infratentorial ependymomas.[120] All untreated patients receive postoperative radiotherapy to the entire cerebrospinal axis with a booster dose of radiation to the posterior fossa. Half of the patients are randomized to concurrent weekly vincristine for 8 weeks followed by eight 6-week cycles of combination chemotherapy with CCNU, prednisone, and vincristine. In a second study, patients who have relapsed following surgery and radiotherapy are crossed over to treatment with CCNU, vincristine, and procarbazine, while those relapsing after surgery, radiotherapy, and chemotherapy are crossed over to treatment with procarbazine alone. Additional radiotherapy is given if the relapse has occurred greater than 1 year from diagnosis. To date there is no difference between the two regimens in terms of disease-free survival or overall survival.

Multiple myeloma

Nitrosoureas have been studied in multiple myeloma as part of initial remission induction therapy, in patients who had late relapses following objective remissions with standard alkylating agents such as L-phenylalanine mustard (melphalan) or cyclophosphamide and in patients who have never gained an initial objective response to these drugs.

Cancer and Acute Leukemia Group B (CALGB), comparing BCNU plus prednisone to melphalan plus prednisone induction therapy, noted an equal response in both groups (40% versus 41%) with an overall median survival for the responders of 30 months.[122] Increased marrow toxicity in the BCNU-prednisone arm in conjunction with the lower cost and ease of administration of melphalan-prednisone make the latter arm more preferable. The recent joint ECOG/Southeast Group study comparing BCNU-cyclophosphamide-*prednisone against melphalan-prednisone* in previously untreated patients thus far has shown no superiority in terms of median survival in the three-drug arm.[123] Similarly, the Canadian National Cancer Institute study comparing combination melphalan-cyclophosphamide-BCNU and prednisone induction therapy for previously untreated myeloma patients to melphalan-prednisone alone has shown no significant difference in terms of median survival among the different treatment groups.[124]

In an uncontrolled study at Memorial Hospital using a five-drug regimen of melphalan, cyclophosphamide, BCNU, prednisone, and vincristine (M_2 protocol), objective remissions were obtained in 40/46 (87%) untreated myeloma patients with a median duration of response of 20+ months and an expected median survival of 34+ months.[125] In addition, 13/26 (50%) previous "failures" were reported to respond with a median response duration of 22+ months.

Remission maintenance with BCNU or melphalan for patients who enter "complete remission" (defined as greater than 75% tumor regression) was

studied by Alexanian et al. in the SWOG.[129] They noted that remission duration and survival were statistically identical in patients randomly assigned to maintenance melphalan plus prednisone, BCNU plus prednisone, or no further treatment.

The response rate to single-agent nitrosourea therapy in refractory myeloma is limited to an occasional dramatic response. However, the combination of BCNU plus adriamycin may be promising. This combination was used in a pilot study to treat 43 patients who did not respond initially or who were in relapse after remission produced by alkylating agent-prednisone therapy.[127] Seven of the 43 patients responded, two with complete clinical remissions and a greater than 75% reduction in tumor cell mass lasting 12–16 months. Five others had partial remission with lesser degrees of tumor mass reduction and improvement in bone pain.

SWOG is currently evaluating a four-drug combination regimen of BCNU, adriamycin, vincristine, and prednisone in patients who have relapsed on melphalan and/or cyclophosphamide therapy and in patients who never achieved initial remission with standard alkylating drugs.[122,128] Of 29 patients who had relapsed on melphalan and/or cyclophosphamide, 9 (31%) have achieved a partial remission as evidenced by >50% decrease in the serum paraprotein or a decrease in Bence Jones urinary protein to less than 200 mg per 24 hours. Of six patients never responding to conventional treatment, one has responded to the quadruple chemotherapy regimen.

Lymphomas

Initial reports of the antitumor activity of the nitrosoureas in malignant lymphoma were first noted in 1965 by DeVita.[29] The following decade defined a therapeutic role for BCNU and CCNU as secondary chemotherapeutic agents in the treatment of both Hodgkin's and non-Hodgkin's lymphoma. Clinical trials aimed at incorporating these nitrosoureas into initial combination chemotherapy regimens have been instituted in previously untreated patients, but the results have not established a definitive role for either BCNU or CCNU in primary treatment regimens.

Hodgkin's disease

The cumulative reported response rates for the nitrosoureas in previously treated Hodgkin's disease are 11% for BCNU,[129] 48% for CCNU,[33] and 26% for methyl CCNU.[33] Cancer and Acute Leukemia Group B (CALGB) directly compared the efficacy of CCNU versus BCNU in patients with advanced Hodgkin's disease who were refractory or unresponsive to prior chemotherapy.[33] The overall response to BCNU (25% of 5–19 patients) was significantly less than CCNU (73% in 16/22 patients). Twenty-three percent of the patients given CCNU achieved a complete remission. Sequential trials of BCNU and methyl CCNU by the Southeastern Oncology Group (SEG) have demonstrated inferior single-agent activity for methyl CCNU, and this agent is now rarely used in the treatment of Hodgkin's disease.[130] Of interest is the recent report by Harrison and Neiman[131] who used BCNU as initial single-agent chemotherapy for disseminated IIIB (one patient) and IVB (10 patients) Hodgkin's disease. Complete remissions were achieved in 7/11 patients and three are alive and disease-free after 69, 77, and 94 months.

MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) is the standard therapeutic regimen for previously untreated patients with stage IIIB and IV Hodgkin's disease.[132] There has been considerable interest in incorporating the nitrosoureas into newer combination regimens in an attempt to provide an effective alternative to MOPP. ECOG compared MOPP to a five-drug regimen, BCVPP (BCNU, cyclophosphamide, vinblastine, procarbazine, and prednisone) in advanced Hodgkin's disease.[133] There was no significant difference between the induction programs in achieving complete remissions (76% with MOPP, 75% with BCVPP). Two-year durations of complete remissions were similar (MOPP 66%, BCVPP 73%) as were 2-year survivals (MOPP 77%, BCVPP 75%). Analysis of the maintenance phase shows similar 2-year complete remission durations (BCVPP 77%, BCG 70%, no therapy 69%) and similar 2-year survivals (90%, 89%, and 96% respectively). Severe gastrointestinal toxicity and neurotoxicity was less with BCVPP induction although hematologic toxicity was similar.

The SEG achieved a 68% complete response with BCVPP.[130] Their initial data suggested that six additional cycles of BCVPP or MOPP chemotherapy in patients achieving complete remission was advantageous in terms of increasing both disease-free survival and overall survival. However,

a recent update[41] revealed no advantage for maintenance chemotherapy over concurrent controls who were unmaintained. These data confirm the results of a National Cancer Institute trial which did not demonstrate a role for maintenance chemotherapy with either MOPP or with single agent BCNU in patients achieving MOPP induced complete remissions.[139]

CCNU has also been incorporated into induction combination regimens for previously untreated patients but final results from these controlled trials are pending. Preliminary results from a prospective CALGB study in patients with both untreated and previously treated stage III and IV Hodgkin's disease comparing MOPP, MVPP (nitrogen mustard, vinblastine, procarbazine, prednisone), CCNU plus OPP, and CCNU plus VPP have suggested a greater number of complete remissions in the "prior therapy" group receiving CCNU combination therapy as compared to nitrogen mustard.[145] In addition CCNU containing regimens were associated with longer maintained remissions.

A variety of CCNU-containing combinations with adriamycin, bleomycin, vinblastine, streptozotocin, and prednisone have been developed for patients with MOPP-resistant Hodgkin's disease. They achieve partial remissions in 59–85% of the patients.[136–142]

Non-Hodgkin's lymphomas

Reported overall response rates for the nitrosoureas in non-Hodgkin's lymphomas are 28% for BCNU,[49] 28% for CCNU,[43] and 18% for methyl CCNU.[43] BCNU has been studied extensively as part of initial combination chemotherapy regimens in previously untreated patients. ECOG compared cyclophosphamide prednisone induction to BCNU prednisone induction in patients with nodular and diffuse well or poorly differentiated lymphocytic lymphoma and demonstrated no significant differences in complete and partial response rates.[143] The complete response rate with BCNU–prednisone of 18% was significantly inferior to that achieved with other non-nitrosourea combination regimens.[143] In addition, there was no cross resistance in those patients who failed induction with either regimen. The four-drug combination of BCVP (BCNU, cyclophosphamide, vincristine, and prednisone) appeared superior to chlorambucil alone in the second or maintenance phase of this ECOG trial by the higher percentage of complete responses obtained and fewer relapses seen on the intensive BCVP arm.[143] In patients with nodular and diffuse histiocytic lymphoma, ECOG again evaluated BCVP and achieved a 33% complete remission rate in these unfavorable histologies.[143] The SEG also studied the BCVP combination in diffuse histiocytic lymphoma, achieving a 50% complete remission rate (patients were not rigorously restaged in either the ECOG or SEG studies, however).[144] ECOG has recently completed protocols utilizing BCVP in one arm as both an induction and maintenance regimen for patients with all histologic subtypes of non-Hodgkin's lymphomas.

In a study of patients with nodular pattern lymphoma of all histologies and diffuse well-differentiated lymphocytic lymphomas,[145] BCVP yielded a complete response rate of 50% compared to 32% for CP and 53% for CVP plus procarbazine (CVPP). One-year percentages of survival were 77% for BCVP, 95% for CP and 86% for CVPP, suggesting that for favorable non-Hodgkin's lymphomas moderate treatment with cyclophosphamide plus prednisone is as effective as the more intensive four-drug regimens.

In unfavorable diffuse histology non-Hodgkin's lymphomas,[146] BCVP was compared to CVP plus adriamycin and to CVP plus bleomycin, the bleomycin being given in two different schedules. Complete responders were then randomized to no therapy or BCVP for 1½ years. Initial results indicate that the CVP plus adriamycin induction arm provides a higher percentage of complete remissions as well as longer median response duration and overall survival compared to the BCVP arm and one of the two CVP plus bleomycin arms. Toxicity was more frequent with BCVP than in the other three arms. The maintenance phase of the study is on-going but no survival differences are as yet apparent in the group of complete responders.

Discussion

The nitrosoureas, BCNU, CCNU, and methyl CCNU, have a wide range of activity in human malignancies. They were synthesized as part of the National Cancer Institute's drug screening program and have undergone extensive evaluation in both animal and human neoplasms. Nitrosoureas may

rk by multiple mechanisms. They have the
ility *in vitro* to act as alkylating agents, to car-
ylate proteins, to inhibit one-carbon metabo-
m, and to interfere with the synthesis of purine
cleotides. Pharmacokinetic studies demonstrate
id gastrointestinal absorption, prolonged plasma
els, and cerebrospinal fluid penetration. The
ent nitrosoureas appear to be inactive com-
unds but the active metabolites remain unidenti-
ed. The long duration of action and delayed
elosuppression are unexplained although tissue
ake with slow release of the active metabolites
s been postulated.

Nitrosoureas may be administered every 6–8
eeks in a single-dose schedule. It must be stressed
at severe hematologic-related toxicity was com-
on in early clinical and animal studies. Nitro-
ureas may cause long-duration peripheral cyto-
enias, unpredictable blood count nadirs, and cu-
ulative marrow toxicity. Complete blood counts
ust be monitored at least once a week during ni-
osourea therapy and preferable twice a week in
atients demonstrating both early and late nadirs.
itrosoureas are especially myelosuppressive in
atients previously treated with chemotherapy
d or radiotherapy. Recently described fatal
lmonary toxicity, chronic renal failure, and the
otential leukemogenic effects need further close
ntiny.

As single agents, nitrosoureas have their best
ctivity in Hodgkin's disease and malignant lym-
phoma. They appear to achieve objective remis-
ns in patients with recurrent malignant glioma
eviously treated with surgery and radiotherapy.
heir role remains to be defined as part of initial
ombined modality therapy in newly diagnosed
atients with glioma.

**BCNU–prednisone initial remission induction
herapy in myeloma compares favorably with
elphalan prednisone but is fraught with in-
reased toxicity. The efficacy of BCNU-containing
egimens in refractory myeloma is under investi-
ation but appears promising.** The nitrosoureas
CNU and methyl CCNU can be considered
rst-line drugs in patients with disseminated ma-
gnant melanoma and produce response rates
quivalent to that seen with DTIC. Surprisingly,
itrosoureas are not additive to DTIC in terms of
mproved response rates, and as single agents have
o efficacy in the treatment of central nervous
stem metastases from melanoma.

An area of great interest involves use of ni-
trosourea–5-fluorouracil combinations as adjuvant
therapy in gastric and colorectal cancer. Response
rates in patients with advanced gastric and colo-
rectal cancer are often increased as compared to
single agent 5-fluorouracil therapy. It is hoped that
this observation can be translated into prolonged
survival in patients with a more limited disease who
are at high risk of recurrence following definitive
surgery. At present, nitrosourea–fluorouracil
combination therapy should not be considered
standard therapy in metastatic gastrointestinal
malignancy because of the failure to document
improved survival.

Nitrosoureas have their major role as part of
combined modality therapy in patients with dis-
seminated or advanced "localized" malignancies.
In addition, newer analogs of the nitrosoureas are
being synthesized and clinical phase I–II trials with
chlorozotocin have recently been initiated.[117,118]
This compound belongs to a class of nitrosourea
analogs which possess glycosidic side groups. It has
significant antitumor activity against L1210 leu-
kemia and produces only a minor degree of inhi-
bition of mouse and human bone marrow DNA
synthesis compared to BCNU.[119] The three nitro-
soureas reviewed in this paper, plus streptozotocin
and now chlorozotocin, are major additions to the
chemotherapist's arsenal. Hopefully, further studies
will better identify the optimal role of nitrosoureas
in the treatment of patients with cancer.

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References

1. Carter, S. K., Schabel, F. M., Broder, L. E., et al.: 1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU) and other nitrosoureas in cancer treatment: a review. *Adv. Cancer Res.* 16: 273–331, 1972.
2. Schabel, F. M., Jr., et al.: 1,3-bis-2-chloroethyl-1-nitrosourea: cancer spectrum of tumors. *Proc. Am. Assoc. Cancer Res.* 6: 62, 1965.
3. Broder, L. E., and Carter, S. K.: Pancreatic islet cell carcinoma I. Clinical features of 32 patients. *Ann. Intern. Med.* 79: 101–107, 1973.
4. Broder, L. E., and Carter, S. K.: Pancreatic islet cell carcinoma II. Results of therapy with streptozotocin in 32 patients. *Ann. Intern. Med.* 79: 108–118, 1973.

5 Greene M O and Greenberg J The activity of nitrosoguanidines against ascites tumor in mice *Cancer Res 20: 1166-1172, 1960*

6 Skipper, H E Schabel, F M Trader M W et al Experimental evaluation of potential anticancer agents VI Anatomic distribution of leukemia cells and failure of chemotherapy *Cancer Res 21: 1154-1164, 1961*

7 Schabel F M Johnston T P McCoich G S et al Experimental evaluation of potential anticancer agents VIII Effects of certain nitrosoureas on intracerebral L1210 leukemia *Cancer Res 23: 725-733 1963*

8 Schabel F M In vivo leukemia cell kill kinetics and "curability" in experimental systems In *The Proliferation and Spread of Neoplastic Cells, Twenty-First Annual Symposium on Fundamental Cancer Research, 1967* The University of Texas M D Anderson Hospital and Tumor Institute at Houston Williams and Wilkins Baltimore, 1967 pp 379-408

9 Mavo, J G Laster, W R Andrews, C M et al Success and failure in the treatment of solid tumors III "Cure" of metastatic Lewis lung carcinoma with methyl CCNU (NSC 95441) and surgery chemotherapy *Cancer Chemother Rep 56: 185-195 1972*

10 Wheeler G P Bowdon, B J Adamson, D J et al Effects of 1,3-bis(2-chloroethyl)-1-nitrosourea and some chemically related compounds upon the progression of cultured HEp No 2 cells through the cell cycle *Cancer Res 30: 1817-1827 1970*

11 Schmall B Cheng D J Fujimura S et al Modification of proteins by 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC 79037) with nucleic acids and proteins in vitro *Cancer Res 32: 22-27, 1972*

12 Chang C J Fujimura S Grunberger, D et al Interaction of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC 79037) with nucleic acids and proteins in vivo and in vitro *Cancer Res 32: 22-27 1972*

13 Wheeler G P and Bowdon B J Effects of 1,3-bis(2-chloroethyl)-1-nitrosourea upon the synthesis of protein and nucleic acids in vivo and in vitro *Cancer Res 25: 1770-1778, 1965*

14 Wheeler G P and Chumley S Alkylating activity of 1,3-bis(2-chloroethyl)-1-nitrosourea and related compounds *J Med Chem 10: 259-261, 1967*

15 Jensen D E and Reed D J Direct evidence for DNA phosphotriester formation by nitrosoureas *Proc Am Soc Clin Oncol 18: 72 1977*

16 Gale G R Effect of 1,3-bis(2-chloroethyl)-1-nitrosourea on Ehrlich ascites tumor cells *Biochem Pharmacol 14: 1705-1710 1977*

17 Wheeler G P and Bowdon B J Effects of 1,3-bis(2-chloroethyl)-1-nitrosourea and related compounds upon the synthesis of DNA by cell free systems *Cancer Res 28: 52-59 1968*

18 Shirakawa S and Lee Comparative effects of the antitumor agents 5-(dimethyltriazeno) imidazole-4-carboxamide and 1,3-bis(2-chloroethyl)-1-nitrosourea on cell cycle of L1210 leukemia cells in vivo *Cancer Res 30: 2174-2179 1970*

19 Grab D P D'Angelo J M Vogler W R et al Selective metabolic effects of 1,3-bis(2-chloroethyl)-1-nitrosourea upon de novo purine biosynthesis *Cancer Res 31: 332-336, 1971*

20 Oliverio V T Toxicology and pharmacology of the nitrosoureas *Cancer Chemther Rep 4: 13-20 1973*

21 DeVita V T Denham C Davidson J D et al The physiological disposition of the carcinostatic 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in man and animals *Clin Pharmacol Ther 8: 566-577, 1967*

22 Sponzo R W DeVita V T and Oliverio, V T Physiologic disposition of 1-(2-chloroethyl)-3-(4-methyl cyclohexyl)-1-nitrosourea (MeCCNU) in man *Cancer 31: 1154-1159, 1973*

23 Oliverio, V T Vietzke W M Williams, M K et al The absorption, distribution, excretion and biotransformation of the carcinostatic 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea in animals *Cancer Res 20: 1330-1337, 1970.*

24 Brav, D Oliverio, V Adamson, R et al Cell cycle effects produced by 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and its decomposition products *Proc Am Assoc Cancer Res 11: 12, 1970*

25 Luo, T L Dion, R L Dixon, R L et al The antitumor agent 1,3-bis(2-chloroethyl)-1-nitrosourea *J Pharm Sci 55: 492-497, 1966*

26 Wasserman T H The nitrosoureas: An outline of clinical schedule and toxic effects *Cancer Treat Rep 60: 709-711, 1976*

27 Moertel C G Therapy of advanced gastrointestinal cancer with the nitrosoureas *Cancer Chemother Rep 1: 27-34, 1973*

28 Young, R C Walker, M D Cancellos, G P et al Initial clinical trials with methyl CCNU (1-(2-chloroethyl)-3-(4-methyl cyclohexyl)-1-nitrosourea *Cancer 31: 1161-1169 1973*

29 DeVita V T Carbone P P and Owens A H et al Clinical trials with 1,3-bis(2-chloroethyl)-1-nitrosourea NSC 409962 *Cancer Res 25: 1876-1881 1965*

30 Lessner, H E BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea): Effects on advanced Hodgkin's disease and other neoplasia *Cancer 22: 451-456, 1968*

31 Schorer A E Oken M M and Johnson, G J Cryptococcosis with nitrosourea therapy *Cancer Treat Rep 62: 574-576, 1978*

32 Durant J R Norgard M J Murad T M et al Pulmonary toxicity associated with bischloroethyl nitrosourea (BCNU) *Ann Intern Med 90: 191-194 1979*

33 Holoye P Y Jenkins D E and Greenberg S D Pulmonary toxicity in long-term administration of BCNU *Cancer Treat Rep 60: 1691-1694 1976*

34 Bailey C C Marsden H B and Morris Jones P H et al pulmonary fibrosis following 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) therapy *Cancer 42: 74-76, 1978*

35 Selker R G Jacobs S A and Moore P Interstitial pulmonary fibrosis as a complication of 1,3-bis(2-

chloroethyl)-1-nitrosourea (BCNU) therapy. *Proc Am Assoc Clin Oncol 19*: 343, 1978.

36 Willson, J. K. V. Pulmonary toxicity of antineoplastic drugs. *Cancer Treat Rep 62*: 2003–2008, 1978.

37 Bellot, P. A., and Valdiserri, R. O. Multiple pulmonary lesions in a patient treated with BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) for glioblastoma multiforme. *Cancer 43*: 46–50, 1979.

38 Lee, W., Moore, R. P., and Wampler, G. L. Interstitial pulmonary fibrosis as a complication of prolonged methyl CCNU therapy. *Cancer Treat Rep 62*: 1355–1356, 1978.

39 Jensen-Akula, M. Report on renal abnormalities associated with prolonged methyl CCNU therapy. Memorandum from Dept. of Health, Education, and Welfare, National Institutes of Health, February 23, 1979.

40 Harmon, W. E., Cohen, H. J., Schwedeberger, E. E., et al. Chronic renal failure in children treated with methyl CCNU. *N Engl J Med 300*: 1200–1203, 1979.

41 Silver, H. K. B., and Morton, D. L. CCNU nephrotoxicity following sustained remission in oat cell carcinoma. *Cancer Treat Rep 63*: 226–227, 1979.

42 Cohen, B. J., Wiernik, P. H., and Walker, M. D. Acute monocytic leukemia associated with nitrosourea chemotherapy. A report of two cases. *Cancer Treat Rep 60*: 1247–1261, 1976.

43 Wasserman, T. H., Slavik, M., and Carter, S. K. Review of CCNU in clinical cancer therapy. *Cancer Treat Rev 1*: 131–151, 1974.

44 Wasserman, T. H., Slavik, M., and Carter, S. K. Methyl CCNU in clinical cancer therapy. *Cancer Treat Rev 1*: 251–269, 1974.

45 Moertel, C. G., Schutt, A. J., Reitemeier, R. J., et al. Therapy for gastrointestinal cancer with the nitrosoureas alone and in drug combination. *Cancer Treat Rep 60*: 729–732, 1976.

46 Moertel, C. G. Clinical management of advanced gastrointestinal cancer. *Cancer 36*: 675–682, 1975.

47 Carter, S. K. Integration of chemotherapy into combined modality treatment of solid tumors. VII. Adenocarcinoma of the breast. *Cancer Treat Rev 3*: 111–174, 1976.

48 Comis, R. L. DTIC (NSC 45388) in malignant melanoma. A prospective. *Cancer Treat Rep 60*: 165–176, 1976.

49 Wasserman, T. H., Slavik, M., and Carter, S. K. Clinical comparison of the nitrosoureas. *Cancer 36*: 1258–1268, 1975.

50 Goldsmith, M. A., and Carter, S. K. Glioblastoma multiforme—a review of therapy. *Cancer Treat Rev 1*: 153–165, 1974.

51 Moertel, C. G. Natural history of gastrointestinal cancer. In *Advanced Gastrointestinal Cancer: Clinical Management and Chemotherapy*, C. G. Moertel and R. J. Reitemeier, Eds. Harper and Row, New York, 1969, pp. 3–14.

52 Moertel, C. G. Chemotherapy of gastrointestinal cancer. *Clin Gastroenterol 5*: 777–793, 1976.

53 Kovach, J. S., Moertel, C. G., Schutt, A. J., et al. A controlled study of combined BCNU and 5-fluorouracil therapy for advanced gastric and pancreatic cancer. *Cancer 33*: 563–567, 1974.

54 Moertel, C. G., Mittelman, J. V., Bakemeier, R. F., et al. Sequential and combination chemotherapy of advanced gastric cancer. *Cancer 38*: 678–682, 1976.

55 Moertel, C. G., and Lavin, P. T. An evaluation of 5-FU, nitrosourea and "lactone" combinations in the therapy of upper gastrointestinal cancer. *Proc Am Soc Clin Oncol 18*: 311, 1977.

56 O'Connell, M. J., Moertel, C. G., and Lavin, P. T. Adriamycin, 5-fluorouracil plus mitomycin C plus cytosine arabinoside, and 5-fluorouracil, adriamycin plus methyl CCNU in advanced gastric carcinoma. *Proc Am Soc Clin Oncol 19*: 343, 1978.

57 Moertel, C. G., O'Connell, M. J., and Lavin, P. T. Chemotherapy of gastric carcinoma. *Proc Am Assoc Cancer Res 20*: 288, 1979.

58 Buroker, T., Kim, P. N., Heilbrun, N., et al. 5-FU infusion with mitomycin C vs. 5-FU infusion with methyl CCNU in the treatment of upper gastrointestinal cancer. A phase III study. *Proc Am Soc Clin Oncol 19*: 310, 1978.

59 Engstrom, P. F., Catalano, R. B., and Creech, R. W. Phase II study of methyl CCNU (NSC 95441) in advanced gastrointestinal cancer. *Cancer Treat Rep 60*: 285–287, 1976.

60 Cedermark, B. J., Didolkar, M. S., and Elias, E. G. Methyl CCNU (NSC 95441) in advanced colorectal carcinoma after failure of 5-fluorouracil (NSC 19893) therapy. *Cancer Treat Rep 60*: 235–238, 1976.

61 Douglass, H. O., and Moertel, C. Chemotherapy of previously tested colorectal adenocarcinomas with methyl CCNU or beta-2-deoxythioguanosine (BTGDR): a phase II–III study of ECOG. *Proc Am Soc Clin Oncol 17*: 306, 1976.

62 Douglass, H. O., Lavin, P. T., Moertel, C. G., et al. Cyclophosphamide or 6-thioguanine plus 5-fluorouracil vs. methyl CCNU or 5-fluorouracil alone in the treatment of advanced colorectal carcinoma. An Eastern Cooperative Oncology Group (ECOG) study. *Proc Am Assoc Cancer Res 18*: 137, 1977.

63 Moertel, C. G., Schutt, A. J., Hahn, R. G., et al. Therapy of advanced colorectal cancer with a combination of 5-fluorouracil, methyl-1,3-bis (2-chloroethyl)-1-nitrosourea and vincristine. *J Natl Cancer Inst 54*: 69–71, 1975.

64 Falkson, G., and Falkson, H. C. Fluorouracil, methyl CCNU and vincristine in cancer of the colon. *Cancer 38*: 1168–1170, 1976.

65 Baker, L. H., Talley, R. W., Mattox, R., et al. Phase III comparison of the treatment of advanced gastrointestinal cancer with bolus weekly 5-FU vs. methyl CCNU plus bolus weekly 5-FU. *Cancer 38*: 1–7, 1976.

66 MacDonald, J. S., Kestner, D. F., Smythe, T., et al. 5-Fluorouracil, methyl CCNU and vincristine in the treatment of advanced colorectal cancer. Phase II study using weekly 5-FU. *Cancer Treat Rep 60*: 1597–1600, 1976.

67 Engstrom, P., MacIntyre, J., Douglass, H., et al.

Combination chemotherapy of advanced bowel cancer. *Proc Am Soc Clin Oncol 19*: 381, 1978.

68 Moertel, C. G., O'Connell, M. J., Ritts, R. E., et al. A controlled evaluation of combined immunotherapy (MER-BCG) and chemotherapy for advanced colorectal cancer. In *Immunotherapy of Cancer: Present Status of Trials in Man*, W. D. Terry and D. Windhorst, Eds. Raven Press, New York, 1978, pp. 573–586.

69 Buroker, T., Kim, P. N., Groppe, C., et al. 5-FU infusion with mitomycin C vs. 5-FU infusion with methyl CCNU in the treatment of advanced colon cancer. *Cancer 42*: 1228–1233, 1978.

70 Lokich, J. J., Skarin, A. T., Mayer, R. J., et al. Lack of effectiveness of combined 5-fluorouracil and methyl CCNU therapy in advanced colorectal cancer. *Cancer 40*: 2792–2796, 1977.

71 Fischeth, M. B., Carey, R. W., Weitzman, S. A., et al. Treatment of advanced colorectal cancer with a combination of 5-fluorouracil and methyl CCNU. *Med Pediatr Oncol 4*: 277–278, 1978.

72 Kane, R. C., Cashdollar, M. R., and Bernath, A. M. Treatment of advanced colorectal cancer with methyl CCNU plus 5-day 5-fluorouracil infusion. *Cancer Treat Rep 62*: 1521–1525, 1978.

73 Kemeny, N., Yagoda, A., Braun, D., et al. A randomized study of two different schedules of methyl CCNU, 5-FU and vincristine for metastatic colorectal cancer. *Cancer 43*: 78–82, 1979.

74 Kemeny, N., Yagoda, A., and Gollbey, R. Methyl CCNU, 5-fluorouracil, vincristine and streptozotocin (MOF-STREP) for metastatic colorectal carcinoma. *Proc Am Assoc Clin Oncol 19*: 345, 1978.

75 Greco, F. A., Richardson, R. L., Schulman, S. F., et al. Combination of constant infusion 5-fluorouracil, methyl CCNU, mitomycin C and vincristine in advanced colorectal carcinoma. *Cancer Treat Rep 62*: 1107–1108, 1978.

76 Shaw, M. T., and Heilbrun, L. K. Baker's antifol in combination with methyl CCNU and 5-fluorouracil for the treatment of metastatic colorectal cancer. *Proc Am Soc Clin Oncol 20*: 400, 1979.

77 Perry, M. C., White, L., and Kardinal, C. 5-Fluorouracil, methyl CCNU and dianomycin in advanced colorectal adenocarcinoma. *Proc Am Soc Clin Oncol 20*: 328, 79.

78 Lokich, J. J. Adjuvant therapy for surgically curable colon cancer: A controlled study of chemo and immune therapy. *Proc Am Soc Clin Oncol 20*: 423, 1979.

79 Davis, H. L., and Kistner, D. L. Analysis of adjuvant therapy in large bowel cancer. *Cancer Clin Trials 1*: 273–287, 1978.

80 Stephens, R. L., Hoogstraten, B., Haas, C., et al. Pancreatic cancer treated with carmustine, fluorouracil and spironolactone. *Arch Intern Med 138*: 115–117, 1978.

81 Bellet, R. E., Mastrangelo, M. J., Berd, D., et al. Melanoma chemotherapy. In *Cancer Chemotherapy III*, I. Brodsky and S. B. Kahn, Eds., Grune and Stratton, New York, *in press*.

82 Carbone, P. P., and Costello, W. Eastern Cooperative Group Studies with DTIC (NSC 45388). *Cancer Treat Rep 60*: 193–198, 1976.

83 Nathanson, L., Cunningham, T., Kupernunc, M., et al. Combination chemoimmunotherapy of malignant melanoma. *Proc Am Soc Clin Oncol 20*: 314, 79.

84 McKelvey, E. M., Luce, J. K., Talley, R. W., et al. Combination chemotherapy with BCNU, vincristine and DTIC in disseminated malignant melanoma. *Cancer 39*: 1–4, 1977.

85 McKelvey, E. M., Luce, J. K., Vaitkevicius, V. K., et al. BCNU, vincristine, DTIC and chlorpromazine combination chemotherapy in disseminated malignant melanoma. *Cancer 39*: 5–10, 1977.

86 Costanzi, J. J. Chemotherapy and BCG in the treatment of disseminated melanoma: A Southwest Oncology Group Study. *Proc Am Soc Clin Oncol 16*: 111, 1977.

87 Costanzi, J. J., Al-Sarraf, M., Dixon, D. O., et al. Chemoimmunotherapy for disseminated melanoma– a SWOG study. *Proc Am Soc Clin Oncol 20*: 362, 1979.

88 Costanzi, J. J., Vaitkevicius, V. K., Quagliana, J. M., et al. Combination chemotherapy for disseminated malignant melanoma. *Cancer 35*: 342–346, 1975.

89 Muss, H. B., White, D. R., Richards, F., et al. Adriamycin and CCNU in the treatment of advanced breast cancer. *Cancer Treat Rep 60*: 1687–1689, 1976.

90 Wall, R. W., Saiki, J. H., Tramm, B. L., et al. Adriamycin and CCNU in advanced breast cancer. *Cancer Clin Trials 1*: 9–11, 1978.

91 Waterfield, W. C., Tashima, C. K., Hortobagyi, G. N., et al. Adriamycin and CCNU in the treatment of metastatic breast cancer. *Cancer 41*: 1235–1239, 1978.

92 Tormey, D. C. Adriamycin (NSC 123127) in breast cancer: An overview of studies. *Cancer Chemother Rep 6*: 319–327, 1975.

93 Presant, C. A., Kolhouse, J. F., and Klahr, C. Adriamycin, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, NSC 409962) and cyclophosphamide in refractory adenocarcinoma of the breast and other tumors. *Cancer 37*: 620–628, 1976.

94 Boston, B., Mitchell, M., Farber, L., et al. Combination vs. combination-sequential non-hormonal chemotherapy in advanced breast cancer. *Proc Am Assoc Cancer Res 17*: 247, 1976.

95 Lloyd, R. F., Salmon, S. E., Jones, S. E., et al. Randomized trial of low-dose adriamycin and cyclophosphamide plus calusterone for advanced breast cancer. *Proc Am Assoc Cancer Res 17*: 126, 1976.

96 Veterans Administration Lung Group Biostatisticians' Report prepared for the 47th Meeting of VALG, Denver, Colorado, May 19–20, 1977.

97 Edmonson, J. H., Lagakos, S., Stolbach, L., et al. Mechlorethamine (NSC 762) plus CCNU (NSC 79037) in treatment of inoperable squamous and large cell carcinoma of the lung. *Cancer Treat Rep 60*: 625–627, 1976.

98 Edmonson, J. H., Lagakos, S. W., Selawry, O. S., et al. Cyclophosphamide and CCNU in the treatment of inoperable small cell carcinoma and adenocarci-

noma. 1976.

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noma of the lungs. *Cancer Treat Rep* 60: 925–932, 1976.

101 Creech R. H., Seydel H. G., Miethlowski W., et al.: Radiation therapy and chemotherapy of localized small cell carcinoma of the lung. *Proc Am Soc Clin Oncol* 20: 313, 1979.

102 Hansen H. H., Selawry O. S., Simon R., et al.: Combination chemotherapy of advanced lung cancer. *Cancer* 38: 2201–2207, 1976.

103 Presant, C. A., Klahr C., Olander J., et al.: Amphotericin B plus BCNU in advanced neoplasia. *Proc Am Assoc Cancer Res* 17: 7, 1977.

104 Presant C. A., Klahr C., and Santala R.: Amphotericin B induction of sensitivity to adriamycin, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), plus cyclophosphamide in human neoplasia. *Ann Intern Med* 86: 47–51, 1977.

105 Samson M. K., Baker L. H., Erode R. J., et al.: Combination chemotherapy with cyclophosphamide, vincristine, methyl CCNU, and bleomycin in advanced bronchogenic carcinoma: Experience with 106 patients. *Cancer Treat Rep* 61: 59–64, 1977.

106 Chalaman A. P., Mandel F., Holland J. F., et al.: MACC (Methotrexate, adriamycin, cyclophosphamide, and CCNU) in advanced lung cancer. *Cancer* 43: 1590–1597, 1979.

107 Livingston R. B., Endicott L. H., Burgess M. A., et al.: Combination chemotherapy with bleomycin (NSC 125066), adriamycin (NSC 123127), CCNU (NSC 79037), vincristine (NSC 67574), and mechlorethamine (NSC 762) (BACON) in squamous cell lung cancer: Experience with 50 patients. *Cancer Chemother Rep* 6: 361–367, 1975.

108 Alexander M., Glatstein E. J., Gordon D. S., et al.: Combined modality therapy for oat cell carcinoma of the lung: A randomized trial. *Cancer Treat Rep* 61: 1–6, 1977.

109 Walker J. D.: Nitrosoureas in central nervous system tumors. *Cancer Chemother Rep* 1: 21–26, 1975.

110 Levin V. A., and Wilson C. B.: Nitrosourea chemotherapy for primary malignant gliomas. *Cancer Treat Rep* 60: 719–724, 1976.

111 Levin V. A., and Wilson C. B.: Chemotherapy: the agents in current use. *Semin Oncol* 2: 63–67, 1975.

112 Wilson C. B., Boldrey E. B., and Enot, K. J.: 1,3-bis(2-chloroethyl)-1-nitrosourea (NSC 409962) in the treatment of brain tumors. *Cancer Chemother Rep* 54: 273–281, 1970.

113 **Rosenblum, M. L.**, Reynolds, A. F., Smith K. A., et al.: Chloroethylcyclohexyl-nitrosourea (CCNU, NSC 79037). *Cancer Chemother Rep* 56: 121–127, 1972.

114 Levin, V. A., Hoffman, W. F., Fischer T. J., et al.: BCNU-5-fluorouracil combination therapy for recurrent malignant brain tumors. *Cancer Treat Rep* 62: 2071–2076, 1978.

115 Avellanosa, A. M., Higby, D. J., and West C. R.: The effectiveness of methyl CCNU, procarbazine, and vincristine in the treatment of non-irradiated malignant gliomas. *Proc Am Soc Clin Oncol* 19: 347, 1978.

116 Walker M. D., Alexander E., Hunt W. E., et al.: Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. *J Neurosurg* 49: 333–343, 1978.

117 Walker M. D., and Strike T. A.: An evaluation of methyl CCNU, BCNU, and radiotherapy in the treatment of malignant glioma. *Proc Am Assoc Cancer Res* 17: 1063, 1976.

118 Walker M. D., and Strike T. A.: An interim analysis of methylprednisolone, procarbazine, BCNU, or BCNU plus methyl prednisolone in the treatment of malignant glioma. *Proc Am Assoc Cancer Res* 20: 200, 1979.

119 Reagan T. J., Bisel H. F., Childs D. S., et al.: Controlled study of CCNU and radiation therapy in malignant astrocytoma. *J Neurosurg* 44: 186–190, 1976.

120 Soleto C. L., Monfardini, S., Brambilla, C., et al.: Controlled study with BCNU vs CCNU as adjuvant chemotherapy following surgery plus radiotherapy for glioblastoma multiforme. *Cancer Clin Trials* 2: 13–18, 1979.

121 Horton J., Chang, C. H., and Schoefeld, D.: Combined modality approaches in malignant brain glioma. *Proc Am Assoc Cancer Res* 18: 212, 1977.

122 E.O.R.T.C. Brain Tumor Group: Effect of CCNU on survival rate of objective remission and duration of free interval in patients with malignant brain glioma: Final evaluation. *Eur J Cancer* 14: 851–856, 1978.

123 Evans, A. E., Jenkin, R. D., Ertel, I., et al.: Adjuvant chemotherapy for medulloblastoma, interim report from CCG 942. *Proc Am Soc Clin Oncol* 20: 425, 1979.

124 Salmon, S. E.: Nitrosoureas in multiple myeloma. *Cancer Treat Rep* 60: 789–794, 1976.

125 Cohen, H. J., Abramson, N., Bartolucci, A., et al.: BCNU, cyclophosphamide and prednisone (BCP) vs melphalan and prednisone (MP) in myeloma. *Proc Am Soc Clin Oncol* 17: 280, 1976.

126 Bergsagel D. E., Bailey, A. J., Langley, G. R., et al.: *Treatment of plasma cell myeloma with prednisone* and sequential, alternating or concurrent schedules of melphalan, cyclophosphamide and carmustine. *Proc Am Soc Clin Oncol* 18: 329, 1977.

127 Case D. C., Lee B. J., and Clarkson B. D.: Improved survival times in multiple myeloma treated with melphalan, prednisone, cyclophosphamide, vincristine and BCNU: M-2 protocol. *Am J Med* 63: 897–903, 1977.

128 Alexanian R., Balcerzak S., Haut A., et al.: Southwest Oncology Group: Remission maintenance therapy for multiple myeloma. *Arch Intern Med* 135: 147–152, 1975.

129 Alberts D. S., Durie B. G. M., and Salmon, S. E.: Doxorubicin, BCNU, chemotherapy for multiple myeloma in relapse. *Lancet* 1: 926–928, 1976.

130 Bonnet, J. D., Alexanian R., and Salmon S. E.: Vincristine, BCNU, adriamycin, prednisone combination for treatment of melphalan and cytoxan-resistant multiple myeloma. *Proc Am Soc Clin Oncol* 18: 343, 1977.

129 Anderson T, DeVita V T, and Young R C BCNU (NSC-409962) in the treatment of advanced Hodgkin's disease: Its role in remission induction and maintenance *Cancer Treat Rep 60: 761-767, 1976.*

130 Durant J R, Bartolucci A, Gams R A, et al Southeastern Cancer Study Group Trials with nitrosoureas in Hodgkin's disease *Cancer Treat Rep 60: 781-787, 1976*

131 Harrison D F, and Norman P F Primary treatment of disseminated Hodgkin's disease with BCNU alone and in combination with vincristine, procarbazine and prednisone *Cancer Treat Rep 61: 789-795, 1977*

132 Goldsmith, M A, and Carter S K Combination chemotherapy of advanced Hodgkin's disease: A review *Cancer 33: 1-8, 1974*

133 Bakemeier R F, Costello W G, Horton J, et al Chemoimmunotherapy of Hodgkin's disease *Proc Am Assoc Clin Oncol 20: 392, 1979*

134 Durant, J R, Gams R A, Velez-Garcia E, et al BCNU, Velban, cyclophosphamide, procarbazine and prednisone: BCVPP in advanced Hodgkin's disease *Cancer 42: 2101-2110, 1978*

135 Cooper M R, Spurr C L, Chidewell O, et al The experience of nitrosourea (CCNU)-containing four-drug combination over MOPP in the treatment of stage III and IV Hodgkin's disease *Blood 46: 1011, 1975*

136 Kurnick J E, White M, Ware D E, et al Bleomycin (NSC-125066) and CCNU (NSC-79037) in the combination chemotherapy of MOPP resistant Hodgkin's disease *Cancer Chemother Rep 59: 1147-1150, 1975*

137 Goldman J M, and Dawson A A Combination therapy for advanced resistant Hodgkin's disease *Lancet 2: 1221-1225, 1975*

138 Williams S, Fuhrow L, and Rob R Combination chemotherapy of refractory Hodgkin's disease with adriamycin and CCNU *Proc Am Soc Clin Oncol 18: 269, 1977*

139 Loh K K, Gamble J F, Shullenberger C C, et al Combination chemotherapy in MOPP-resistant Hodgkin's disease *Proc Am Soc Clin Oncol 18: 342, 1977*

140 Porzig K, and Robertson A Treatment of advanced Hodgkin's disease with BCAVe following MOPP failure *Proc Am Soc Clin Oncol 18: 342, 1977*

141 Levi J A, Wiernik P H, and Diggs, C H Combination chemotherapy of advanced previously treated Hodgkin's disease with streptozotocin CCNU, adriamycin and bleomycin *Med Pediatr Oncol 3: 33-40, 1977*

142 Mosso A H, Kerr R O, Braine H G, et al A kinetically designed chemotherapeutic regimen for advanced refractory lymphoma patients *Med Pediatr Oncol 4: 133-139, 1978*

143 Ezdinli F, Pocock S, Berard C W, et al Comparison of intensive vs moderate chemotherapy of lymphocytic lymphoma *Cancer 38: 1060-1068, 1976*

144 Durant J R, Loeb, V, Dorfman R, et al BCNU, cyclophosphamide, vincristine and prednisone (BCOP): A new therapeutic regimen for diffuse histiocytic lymphoma *Cancer 36: 1930-1944, 1975*

145 Ezdinli E, Costello W G, and Silverstein, M N Chemotherapy of prognostically favorably non-Hodgkin's lymphoma *Blood (Suppl) 52: 219, 1978*

146 Johnson G J, Costello W G, Oken M M, et al The value of adriamycin and of mid-cycle treatment in multidrug therapy of unfavorable histology non-Hodgkin's lymphoma *Proc Am Assoc Cancer Res 20: 196, 1979*

147 Golla R J, Tan C T C, and Young C W Phase I trial of chlorozotocin *Cancer Treat Rep 63: 17-20, 1979*

148 Hoth D, Butler T, Wunokur S, et al Phase II study of chlorozotocin *Proc Am Assoc Clin Oncol 19: 851, 1978*

149 Schein P S, Panasa, L, Woolley P V, et al Pharmacology of chlorozotocin, a new nitrosourea antitumor agent *Cancer Treat Rep 60: 801-805, 1976*

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