

2-Chloroethyl-3-sarcosinamide-1-nitrosoarea, a Novel Chloroethylnitrosoarea Analogue with Enhanced Antitumor Activity against Human Glioma Xenografts¹

Daniela Marcantonio, Lawrence C. Panasci,² Melinda G. Hollingshead, Michael C. Alley, Richard F. Camalier, Edward A. Sausville, Donald J. Dykes, Christopher A. Carter, and Louis Malspeis

Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada H3T 1E2 [D. M., L. C. P.]; Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis, and Centers, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, Maryland 21701-8527 [M. G. H., M. C. A., R. F. C., E. A. S., L. M.]; and Southern Research Institute, Birmingham, Alabama 35205 [D. J. D., C. A. C.]

Abstract

Nitrosoareas are among the most widely used agents used in the treatment of malignant gliomas. Here, the activity of 2-chloroethyl-3-sarcosinamide-1-nitrosoarea (SarCNU) was compared with that of 1,3-bis-(2-chloroethyl)-1-nitrosoarea (BCNU), *in vivo* against s.c. implanted SF-295 and U-251 central nervous system (CNS) tumor xenografts. When given *i.v.*, q4d for 3 doses, to athymic mice bearing s.c. SF-295 tumors, SarCNU, at an optimum of 167 mg/kg/dose, produced 9 tumor-free animals of 10 total animals, 1 regression, and no evidence of overt toxicity ($\geq 20\%$ body weight loss). With a similar dosing schedule, BCNU produced no tumor-free animals, six regressions, and one drug-related death at its optimum of 30 mg/kg/dose. Furthermore, SarCNU retained high antitumor activity at two lower dose levels, 66 and 45% of the optimal dose, whereas BCNU demonstrated a progressive loss of antitumor activity at lower doses. Following *p.o.* administration, SarCNU similarly demonstrated antitumor activity that was superior to that of BCNU. In the U-251 CNS tumor model, SarCNU yielded six of six tumor-free animals at 80 mg/kg/dose with *i.p.* administration q.d. for 5 days, starting on day 14, whereas BCNU, at 9 mg/kg/dose, yielded three of six tumor-free mice and one drug-related death. Again, SarCNU resulted in tumor-free animals at 66 and 45% of its optimal dose and was relatively nontoxic, in contrast to BCNU. Results of testing to date indicate that SarCNU is clearly more effective than BCNU against the human CNS tumors SF-295 and U-251 *in vivo*. These results encourage the initiation of clinical trials for SarCNU, in an effort to improve therapeutic approaches to glioma, but clinical trials must determine whether superiority of SarCNU in preclinical models can be extrapolated to patients.

Introduction

Nitrosoareas (BCNU³ and CCNU) are some of the most widely used chemotherapeutic compounds in the treatment of tumors of the CNS (1). The CNUs are non-ionized and relatively lipid soluble, which allows them to cross the blood-brain barrier (2). However, the clinical use of these drugs is restricted by dose-related toxicity, which produces delayed and cumulative myelosuppression (3). Moreover, CNUs do not produce durable long-term responses and, even in

combination with radiation therapy, are not favorable to the survival of most patients (4). The development of novel agents with increased antitumor activity and decreased toxicity is, therefore, imperative to improving the treatment of CNS tumors.

Our study of a new CNU, SarCNU, demonstrates *in vitro* efficacy against gliomas. SarCNU is a CNU analogue containing the amino acid amide, sarcosinamide, within its structure (5). Initial screening in the human tumor cloning assay indicated that SarCNU was more active than BCNU in primary gliomas at equimolar concentrations (6, 7). The theoretical PPC of SarCNU, calculated on the basis of the LD₅₀ in mice, is 68 μM , whereas that of BCNU is 9 μM (6). This correlates with a 7-fold decrease in the myelotoxicity of SarCNU as compared to BCNU in the *in vitro* colony-forming unit, granulocyte-macrophage, assay (7). Antitumor agents that reduce tumor growth to $\leq 30\%$ in the human tumor cloning assay have an excellent chance of producing responses in the patient from whom the tumor was obtained (8). When the data that was obtained with primary glioma specimens at the PPC of each compound was re-examined, SarCNU reduced colony growth to $\leq 30\%$ of control in 10 of 13 glioma specimens, whereas BCNU was active with 1 of 13 glioma specimens. Furthermore, at the PPC, SarCNU was active against the human glioma cell line, SK-MG-1, whereas BCNU was not active (6). These *in vitro* results suggested that SarCNU might be superior to BCNU against human gliomas.

All clinically available CNUs enter tumor cells via passive diffusion (9). SarCNU is unique in that the presence of the sarcosinamide carrier group allows the drug to enter cells via the extraneuronal catecholamine uptake₂ transporter. This accounts for the increased accumulation of SarCNU in the SK-MG-1 glioma cell line and contributes to its enhanced cytotoxicity (10, 11). SarCNU is representative of a potentially new class of anticancer agents that displays increased antitumor activity by exploiting a physiological aspect of the tumor cell.

Here, comparative activities of SarCNU *versus* BCNU were evaluated by the *i.p.*, *i.v.*, and *p.o.* routes in athymic mice with s.c. implanted CNS tumor xenografts. The results of these investigations confirm the activity of SarCNU in CNS tumor models and clearly offer evidence that SarCNU may be a more efficacious chemotherapeutic agent *in vivo* than is BCNU.

Materials and Methods

Animals. Randomly bred female or male athymic (National Cancer Research *nu/nu*) mice were housed on sterile bedding in microisolator cages with water and food provided *ad libitum*. All animal studies were conducted in American Association for the Accreditation of Laboratory Animal Care-approved facilities following United States Public Health Service guidelines. The tumors used were SF-295 and U-251, both human glioma xenografts. The tumors were maintained and evaluated as described previously (12). Briefly,

Received 4/29/97; accepted 7/31/97.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ This work was supported by National Cancer Institute Contracts N01-CM-47000 and N01-CM-57207.

² To whom requests for reprints should be addressed, at Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, 3755 Côte Ste. Catherine, Montreal, Quebec, Canada H3T 1E2. Phone: (514) 340-8260 ext. 5528; Fax: (514) 340-8302.

³ The abbreviations used are: BCNU, 1,3-bis-(2-chloroethyl)-1-nitrosoarea; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosoarea; CNU, chloroethylnitrosoarea; CNS, central nervous system; SarCNU, 2-chloroethyl-3-sarcosinamide-1-nitrosoarea; PPC, peak plasma concentration; T/C, treated *versus* control; MTD, maximally tolerated dose; TFS, tumor-free survivors.

Table 1 Response of advanced-stage s.c. SF-295 CNS tumor xenografts to SarCNU and BCNU following i.v. administration

	Dose ^a (mg/kg/dose)	No. of mice	No. of drug deaths	No. of regressions	No. of tumor-free animals (day 63)	Optimal %T/C ^b (day)	Growth delay ^c [% (T - C)/C]	Net log cell kill ^d
Control	0	20		0	0			
SarCNU	250	10	6	0	4	Toxic		
	167	10	0	1	9	10 (17)	591	8.1
	111	10	0	2	7	9 (17)	521	7.1
BCNU	74	10	0	2	0	7 (17)	395	5.0
	30	10	1	6	0	5 (17)	452	5.9
	20	10	0	0	0	11 (17)	226	2.1
	13	10	0	0	0	36 (17)	64	-0.6
	9	10	0	0	0	66 (17)	19	-1.3

^a Dosing schedule: q4d for 3 doses, starting on day 7.

^b %T/C was calculated by dividing the median treated tumor weight by the median control tumor weight on each observation day and multiplying by 100. The day on which this optimal T/C occurred is shown in parentheses. A %T/C of <40 was considered active.

^c Growth delay is the percentage by which the treated median tumor weight was delayed in achieving the specified tumor size as compared to the controls, as defined in "Materials and Methods."

^d Net log cell kill is an estimate of the number of log₁₀ units of cells killed by the test agent on the dose, route, and schedule used, as defined in "Materials and Methods."

tumors were maintained by mouse passage using serial transfer of 30–40-mg fragments implanted s.c. in the axillary region. When the tumors reached approximately 200 mg in size, treatments were initiated. BCNU was solubilized in 2% ethanol in saline, and SarCNU was solubilized in 0.01 M sodium acetate buffer (pH 4.9) for administration. Both compounds were administered within 30 min of solubilization. Treatment routes and schedules varied among the experiments. Tumor weights were calculated from twice- or thrice-weekly tumor measurements using the formula for a prolate ellipsoid and assuming unit density (1 mm³ = 1.0 mg). The effects of treatment were assessed by

comparing the median tumor weights in the treated mice to those of the vehicle-treated control mice.

Calculations. The optimal %T/C was calculated by dividing the median treated tumor weight by the median control tumor weight on each observation day and multiplying by 100. This calculation was performed each day the tumors were measured, and the optimal value (minimum), obtained after the first course of treatment, was presented. A %T/C of <40 was considered active. Growth delay is expressed as the percentage by which the treated group median tumor weight was delayed in achieving the specified tumor size

Fig. 1. Response of s.c. SF-295 human glioma xenografts in athymic mice to treatment with SarCNU or BCNU administered i.v. by different schedules. All treatment was initiated on day 7 postimplantation, when all mice had established tumors, ranging from 150 to 245 mg in size. There were 20 mice in the control group (●) and 10 mice in each treated group. SarCNU was administered on dosing schedules of q.d. for 1 and 5 days and q4d for 3 doses, at dosages of 223 mg/kg/dose (□; 430% growth delay, no TFS), 67 mg/kg/dose (△; 591% growth delay, 9 of 10 TFS), and 167 mg/kg/dose (▽; 591% growth delay, 9 of 10 TFS), respectively. BCNU was administered on dosing schedules of q.d. for 1 and 5 days and q4d for 3 doses, at dosages of 40 mg/kg/dose (■; 205% growth delay, no TFS), 8 mg/kg/dose (▲; 141% growth delay, no TFS), and 30 mg/kg/dose (▼; 452% growth delay, no TFS), respectively.

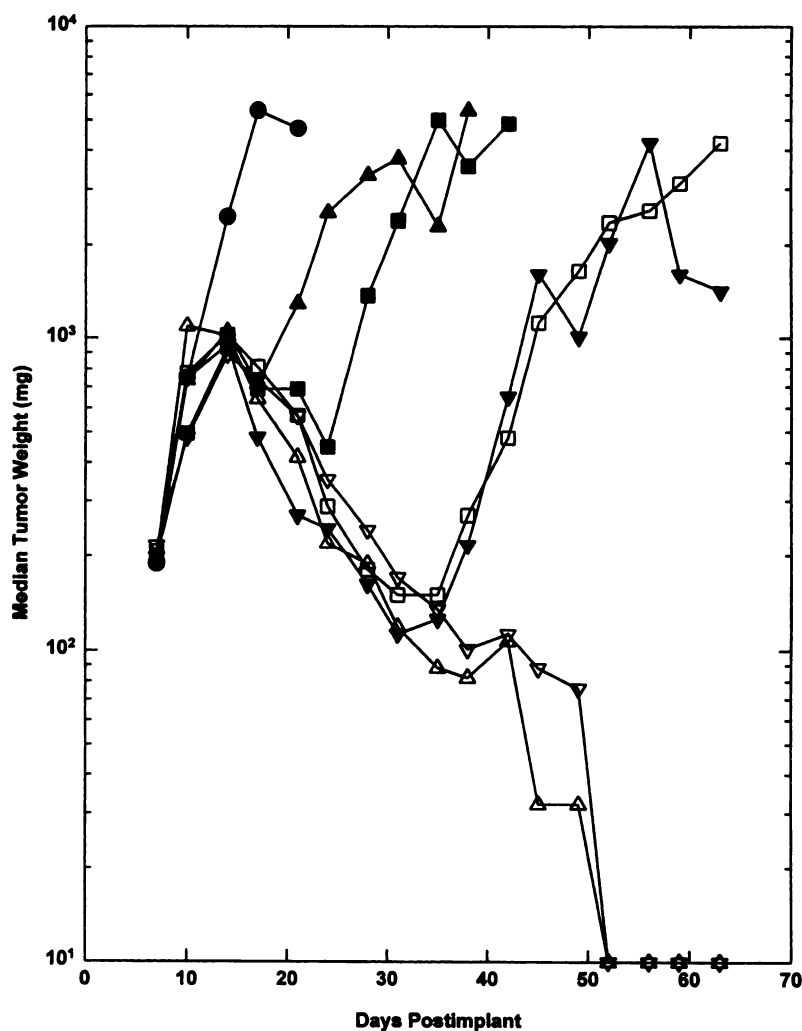


Table 2 Response of advanced-stage s.c. SF-295 CNS tumor xenografts to SarCNU and BCNU following p.o. administration

	Dose ^a (mg/kg/dose)	No. of mice	No. of drug deaths	No. of regressions	No. of tumor-free animals (day 58)	Optimal %T/C ^b (day)	Growth delay ^c [% (T - C)/C]	Net log cell kill ^d
Control	0	17		0				
SarCNU	267	8	4	0	4	Toxic		
	178	8	0	0	8	7 (16)		
	119	8	0	5	0	11 (16)	443	6.9
BCNU	80	8	8	0	0	Toxic		
	53	8	8	0	0	Toxic		
	36	8	6	0	0	Toxic	449	7.1
	24	8	2	0	0	12 (16)	266	3.5

^a Dosing schedule: q4d for 3 doses, starting on day 6.

^b %T/C is calculated by dividing the median treated tumor weight by the median control tumor weight on each observation day and multiplying by 100. The day on which this optimal T/C occurred is shown in parentheses. A %T/C of <40 was considered active.

^c Growth delay is the percentage by which the treated median tumor weight was delayed in achieving the specified tumor size as compared to the controls, as defined in "Materials and Methods."

^d Net log cell kill is an estimate of the number of log₁₀ units of cells killed by the test agent on the dose, route, and schedule used, as defined in "Materials and Methods."

compared to the controls using the formula [(T - C)/C] × 100, where T and C are the median times to a tumor size of x mg for the treated and control groups, respectively. Net log cell kill is an estimate of the number of log₁₀ units of cells killed by the test agent on the dose, route, and schedule used. This value is calculated as {(T-C) - duration of treatment} × 0.301 / doubling time, where the doubling time is the time required for the tumor to increase from 200 to 400 mg. T and C are the median days to reach the specified tumor size, as previously defined.

Results

Antitumor Activity in SF-295 Human Glioma Xenografts after i.v. Administration of SarCNU or BCNU. The i.v. activities of SarCNU and BCNU were examined using a dosing schedule of q4d for 3 doses, with the first treatment on day 7 in SF-295 human glioma-bearing athymic mice (Table 1). SarCNU demonstrated excellent activity in this model. At its highest nontoxic dose of 167 mg/kg, SarCNU resulted in 9 tumor-free mice of a total of 10 mice. The time to complete tumor regression varied from 17 to 48 days after the end of treatment. SarCNU retained its ability to cure animals with less than the MTD. The MTD was 167 mg/kg. At 0.66 × MTD (111 mg/kg), SarCNU resulted in 7 tumor-free animals of a total of 10 animals. At 0.45 × MTD (74 mg/kg), SarCNU retained significant activity, as indicated by the growth delay and the net log cell kill, although no cures were induced. BCNU, at its optimal dose of 30 mg/kg, produced no cures, but there were six regressions and one drug-related death. At its highest nontoxic dose of 20 mg/kg, no cures or regressions were produced, yet BCNU induced a significant growth delay of 226% and a net log cell kill of 2.1, indicating that the drug retained some antitumor activity. At 0.66 × MTD, (13 mg/kg), BCNU retained little antitumor activity.

Antitumor Activity in Relation to Administration Schedules in the SF-295 Model following SarCNU or BCNU Treatment. The antitumor efficacies of SarCNU administered i.v. using three different dosing schedules were compared to that of BCNU in SF-295 human glioma-bearing athymic mice (Fig. 1). Multiple daily dosing schedules of SarCNU, q.d. for 5 days and q4d for 3 doses, at an optimal dose, yielded 9 TFS of 10, whereas a single dose did not result in TFS. In all three schedules, BCNU, at its optimal dose, resulted in no tumor-free animals. With all schedules, SarCNU had an improved therapeutic index over that of BCNU, indicating that SarCNU was more effective.

Antitumor Activity of SarCNU or BCNU following Oral Administration in the SF-295 Model. The oral efficacy of SarCNU was evaluated in the SF-295 model, which demonstrated responsiveness to i.v. administration (Table 2). The bioavailability of SarCNU after oral administration in athymic mice has been demonstrated to be approximately 50% (13). SarCNU, at 267 mg/kg/dose, was excessively toxic. In these mice, there was no visible evidence of damage to the trachea or esophagus. The MTD of 178 mg/kg demonstrated excellent activity, producing delayed tumor regression starting on days 13–20. Some regressions were complete by day 30, and all were complete by day 48. No tumor regrowth had been observed by the time the experiment was terminated on day 58. The 119 mg/kg/day dose level also produced a very good antitumor response, causing three of seven partial regressions and two of seven complete regressions and a large tumor growth delay. All doses of BCNU evaluated were above the MTD. The lowest dose of BCNU, 24 mg/kg/day, caused two of eight drug-related deaths and produced no partial or complete regressions in the surviving mice. In the six surviving mice, a good tumor growth

Table 3 Response of early-stage s.c. U251 CNS tumor xenografts to SarCNU and BCNU following i.p. administration

	Dose ^a (mg/kg/dose)	No. of mice	No. of drug deaths	No. of tumor-free animals (day 59)	Optimal %T/C ^b (day)	Growth delay ^c [% (T - C)/C]	Net log cell kill ^d
Control	0	20		0			
SarCNU	120	6	0	6	0 (28)	N/A ^e	
	80	6	0	6	0 (28)	N/A	
	54	6	0	5	0 (28)	N/A	
	9	6	1	3	0 (42)	102	1.0
BCNU	6	6	0	0	33 (28)	87	0.9
	4	6	0	0	63 (3)	37	0.3

^a Dosing schedule: q4d for 5 doses, starting on day 14.

^b %T/C was calculated by dividing the median treated tumor weight by the median control tumor weight on each observation day and multiplying by 100. The day on which this optimal T/C occurred is shown in parentheses. A %T/C of <40 was considered active.

^c Growth delay is the percentage by which the treated median tumor weight is delayed in achieving the specified tumor size as compared to the controls, as defined in "Materials and Methods."

^d Net log cell kill is an estimate of the number of log₁₀ units of cells killed by the test agent on the dose, route, and schedule used, as defined in "Materials and Methods."

^e N/A, not applicable.

delay was attained, but this effect was smaller than that attained with $0.67 \times$ MTD of SarGNU. These data clearly indicate that p.o. administered SarGNU is more active than p.o. administered BCNU against s.c. implanted SF-295 glioblastomas, under the conditions of testing.

Antitumor Activity of SarGNU or BCNU following i.p. Administration against U-251 Tumor Xenografts. The efficacy of SarGNU versus BCNU using i.p. administration was tested on the U-251 tumor xenograft using the dosing schedule q.d. for 5 days, with initial treatment on day 14 (Table 3). Both the optimal dose of SarGNU, 120 mg/kg, and $0.66 \times$ that dose, resulted in 100% tumor-free animals and produced no toxicity. Furthermore, at $0.45 \times$ MTD, SarGNU resulted in five tumor-free animals of six. In contrast, BCNU, at 9 mg/kg/dose, resulted in one toxic death and three tumor-free animals of six, whereas at $0.66 \times$ and at $0.45 \times$ this dose, there were no tumor-free animals.

Discussion

Here, we show that the antitumor activity of SarGNU is significantly greater than that of BCNU against the s.c. implanted SF-295 and U-251 human CNS tumor xenograft models. The SF-295 tumor expresses low levels of *O*⁶-methylguanine-DNA-methyltransferase (14), whereas U-251 does not have any detectable *O*⁶-methylguanine-DNA-methyltransferase activity (15). Using various routes of administration, including i.v., i.p., and p.o., as well as intermittent or daily dosing schedules, SarGNU, in all cases, cured significantly more animals and was less toxic than BCNU at its optimal dose. The importance of SarGNU as a potential anticancer agent is increased by the fact that it retains excellent antitumor activity at $0.66 \times$ and $0.45 \times$ its optimal dose in mice. Previous studies on the toxicities of anticancer drugs have indicated that humans tolerate less drug on a mg/m² basis than do mice (16). Thus, retention of antitumor activity at less than the MTD in mice suggests potential efficacy in humans. This indicates that SarGNU is a promising agent for the treatment of CNS tumors in humans because it retains excellent antitumor activity at less than the MTD in the murine model.

Previous studies have shown that SarGNU is transported into tumor cells via the extraneuronal catecholamine uptake₂ transporter (10, 11, 17). Therefore, there may be a significant relationship between the dosing schedule and the efficacy of SarGNU. A single dose of SarGNU produced no tumor-free animals. This may be a consequence of saturation of the extraneuronal catecholamine transporter, resulting in an inefficient accumulation of SarGNU in the tumor. Multiple daily dosing schedules, which produced a high cure rate, may allow a kinetic advantage for SarGNU accumulation. The extraneuronal transporter is present in other tissues, including uterus, colon, trachea, and spleen (18). Therefore, SarGNU may be selectively cytotoxic against tumors of other origins in addition to CNS tumors. Investigations will be carried out to determine whether the presence of the uptake₂ carrier correlates with the *in vivo* activity of SarGNU against the SF-295 and U-251 gliomas. Furthermore, identification of tumors expressing the

extraneuronal catecholamine transporter may select tumors with enhanced susceptibility to SarGNU. These results encourage initiation of clinical trials for SarGNU.

References

1. Lesser, G. J., and Grossman, S. The chemotherapy of high-grade astrocytomas. *Semin. Oncol.*, *21*: 220–235, 1994.
2. Walker, M. D., Alexander, E., Jr., Hunt, W. E., MacCarty, C. S., Mahaley, M. S., Jr., Norrell, H. A., Owens, G., Ransohoff, J., Wilson, C. B., Gehan, E. A., and Strike, T. A. Evaluation of BCNU and/or radiation in the treatment of anaplastic gliomas. A comparative clinical trial. *J. Neurosurg.*, *49*: 333–343, 1978.
3. Carter, K. S., Schabel, T. M., Jr., Broler, L. E., and Jonston, T. P. 1,3-bis-(2-Chloroethyl)-1-nitrosourea (BCNU) and other nitrosoureas in cancer treatment: a review. *Adv. Cancer Res.*, *16*: 273–332, 1972.
4. Walker, M. D., Green S. B., Byar, D. P., Alexander, E., Jr., Batzdorf, Mealy, J., Owens, G., Ransohoff, J., Roberston, J. T., Shapiro, W. R., Smith, K. R., Jr., Wilson, C. B., and Strike, T. A. Randomized comparisons of radiation and nitrosoureas for the treatment of malignant glioma after surgery. *N. Engl. J. Med.*, *303*: 1323–1329, 1980.
5. Suami, T., Kato, T., and Hisamatsu, T. 2-Chloroethylnitrosourea congeners of amino acid amides. *J. Med. Chem.*, *25*: 829–832, 1982.
6. Skalski, V., Rivas, J., Panasci, L. C., and Feindel, W. The cytotoxicity of sarcosinamide chloroethylnitrosourea (SarGNU) and BCNU in primary gliomas and glioma cell lines: analysis of data in reference to theoretical peak plasma concentrations in man. *Cancer Chem. Pharmacol.*, *22*: 137–140, 1988.
7. Panasci, L. C., Dufour, M., Chevalier, L., Isabel, G., Lazarus, P., McQuillan, A., Arbit, E., Brem, S., and Feindel, W. Utilization of the HTSCA and CFU-C assay to identify two new 2-chloroethylnitrosourea congeners of amino acid amides with increased *in vitro* activity against human gliomas compared with BCNU. *Cancer Chem. Pharmacol.*, *14*: 156–159, 1985.
8. von Hoff, D. D., Clark, G. M., Stogdill, B. J., Sarosdy, M. F., O'Brien, Casper, J. T., Mattox, D. E., Page, C. P., Cruz, A. B., and Sandbach, J. F. Prospective clinical trial of a human tumor cloning system. *Cancer Res.*, *43*: 1926–1931, 1983.
9. Begleiter, A., Lam, H.-Y. P., and Goldenberg, G. J. Mechanism of uptake of nitrosourea by L5178Y lymphoblasts *in vitro*. *Cancer Res.*, *37*: 1022–1027, 1977.
10. Nöe, A. J., Malapetsa, A., and Panasci, L. C. Altered cytotoxicity of (2-chloroethyl)-3-sarcosinamide-1-nitrosourea in human glioma cell lines SK-MG-1 and SKI-1 correlates with differential transport kinetics. *Cancer Res.*, *54*: 1491–1496, 1994.
11. Nöe, A. J., Malapetsa, A., and Panasci, L. C. Transport of (2-chloroethyl)-3-sarcosinamide-1-nitrosourea in human glioma cell line SK-MG-1 is mediated by an epinephrine sensitive carrier system. *Mol. Pharmacol.*, *44*: 204–209, 1993.
12. Dykes, D. J., Abbott, B. J., Mayo, J. G., Harrison S. D., Jr., Laster, W. R., Jr., Simpson-Herren, I., and Griswold, D. P., Jr. Development of human tumor xenograft models for *in vivo* evaluation of new antitumor drugs. *In: Contributions to Oncology*, Vol. 42, pp. 1–22. Basel: S. Karger AG, 1992.
13. Supko, J. G., Camalier, R. F., Hollingshead, M. G., Grever, M. R., and Malspeis, L. Activity of SarGNU against human CNS tumor xenografts and characterization of its pharmacokinetics in mice. *Proc. Am. Assoc. Cancer Res.*, *36*: 375, 1995.
14. Chen, X. P., Malapetsa, A., McQuillan, A., Marcantonio, D., Bello, V., Mohr, G., Remack, J., Brent, T. P., and Panasci, L. Evidence for nucleotide excision repair as a modifying factor of MGMT-mediated innate chloroethylnitrosourea resistance in human tumor cell line. *Mol. Pharmacol.*, in press, 1997.
15. Dolan, M. E., Mitchell, R. B., Mummert, C., Moschel, R. C., and Pegg, A. Effect of *O*⁶-benzylguanine analogues on sensitivity of human tumor cells to the cytotoxic effects of alkylating agents. *Cancer Res.*, *51*: 3367–3372, 1991.
16. Freireich, E. J., Gehan, E. A., Rall, D. P., Schmidt L. H., and Skipper, H. E. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey and man. *Cancer Chemother. Rep.*, *50*: 219–244, 1966.
17. Panasci, L. C., Marcantonio, D., and Nöe, A. J. SarGNU (2-chloroethyl-3-sarcosinamide-1-nitrosourea): a novel analogue of chloroethylnitrosourea that is transported by the catecholamine uptake₂ carrier, which mediated increased cytotoxicity. *Cancer Chem. Pharmacol.*, *37*: 505–508, 1996.
18. Trendelenburg, U. The extraneuronal uptake and metabolism of catecholamines. *In: U. Trendelenburg and N. Weiner (eds.), Catecholamines 1, Handbook of Experimental Pharmacology*, Vol. 90, pp. 279–319. New York: Springer-Verlag New York, Inc., 1988.

Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

2-Chloroethyl-3-sarcosinamide-1-nitrosourea, a Novel Chloroethylnitrosourea Analogue with Enhanced Antitumor Activity against Human Glioma Xenografts

Daniela Marcantonio, Lawrence C. Panasci, Melinda G. Hollingshead, et al.

Cancer Res 1997;57:3895-3898.

Updated version Access the most recent version of this article at:
<http://cancerres.aacrjournals.org/content/57/18/3895>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://cancerres.aacrjournals.org/content/57/18/3895>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.