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Experimental and Clinical Effect of ACNU in Japan, with Emphasis on Small-cell Carcinoma of the Lung

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Summary. *The experimental and clinical effects of ACNU so far recorded in Japan are reviewed. ACNU was highly effective in leukemia L-1210 and in other types of leukemias, ascites tumors, and solid tumors of mice and rats. On the basis of the results of phase I study, the maximum clinically tolerable single dose of ACNU was 101.8–135.7 mg/m² at a time, and the total acceptable dose was 300–600 mg. The desirable interval between doses was 6–8 weeks. Phase II study revealed that ACNU seemed to be effective against small-cell carcinoma of the lung, brain tumors, Hodgkin's disease, and chronic myelocytic leukemia. In the treatment of small-cell carcinoma of the lung ACNU reduced the rate of brain metastasis and prolonged the survival of patients.*

Introduction

After the development of (1-methyl-1-nitroso-3-nitroguanidine) (MNNG) in 1959, extensive developmental work on the nitrosoureas yielded 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), and 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (methyl-CCNU) one after another in the United States [3]. There are numerous reports on the antitumor effect of these three kinds of nitrosoureas in animal experiments and clinical trials [3]. The definitive spectrum of activity of BCNU, CCNU, and methyl-CCNU as a single agent has been established by the accumulated data of the Cancer Therapy Evaluation Program of the National Cancer Institute in the United States [3, 34, 36]. These three nitrosoureas have recently been used as combined chemotherapeutic agents in brain tumors, Hodgkin's disease, malignant lymphoma, lung cancer, and colorectal cancers. In addition to these nitrosoureas, streptozotocin and chlorozotocin are under clinical trial in the United States [4].

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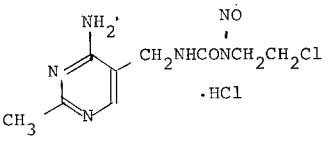

Fig. 1. Structure of ACNU

ACNU (1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride) (Fig. 1) was synthesized in 1974 at the Central Research Laboratory of Sankyo Co. Ltd. by Nakao et al. [1, 31]. ACNU is characterized by its chemical property of being water-soluble, like chlorozotocin in the Phase II study in the United States [4] and unlike the lipid-soluble derivatives such as BCNU, CCNU, and methyl-CCNU. Parenteral administration of BCNU, CCNU, and methyl-CCNU is hampered by their high lipid solubility. ACNU, on the other hand, has a high water solubility as a hydrochloride, and is therefore easily administered by the intravenous route.

The results of an in vitro study of ACNU revealed the possibility that the drug is taken up into cells rapidly to exert its antitumor effect through alkylation of DNA and carbamoylation of proteins [22].

The phase I study of ACNU was finished in Japan in 1974 [5]. Phase II studies followed, with investigation of various kind of tumors. At present, phase III studies of ACNU in combination chemotherapy of small-cell carcinoma of the lungs and gastrointestinal malignancies are under way.

In this report, both the experimental and the clinical data so far recorded on ACNU in Japan are reviewed and the efficacy of ACNU against small-cell carcinoma is discussed with special emphasis.

1. Effect of ACNU on Experimental Tumors

ACNU exerts its antitumor effect against various kinds of experimental tumors, as shown in Table 1. Shimizu and

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Table 1. Maximum effect of ACNU on experimental tumors [12, 28, 31, 32]

Tumors	Animal strain	Effect[a]
Mice tumors		
Leukemia and ascites tumors		
Lymphoid leukemia L1210	BDF_1	+++
Myeloid leukemia C1498	C57BL/6	+++
Plasmacytoma X5563	C3H/He	+++
Ehrlich ascites carcinoma	ICR/JCL	+++
Sarcoma 37	ICR/JCL	±
Mammary tumor MM102	C3H/He	++
Mammary tumor FM3A43	C3H/He	+++
Solid tumors		
Plasmacytoma	C3H/He	+++
Ehrlich carcinoma	ICR/JCL	++
Sarcoma 37	BDF_1	±
Adenocarcinoma 755	BDF_1	±
Meningeal sarcoma MS147	BDF_1	++
Rat tumors		
Ascites tumors		
AH13, AH130, AH44	Donryu	+++
Solid tumor		
Sato lung carcinoma	Donryu	+++

[a] Antitumor activity of the compound was assessed as the increase in lifespan over that of the controls in ascites tumors, and as the reduction in tumor diameter relative to that of the control on the 14th day after transplantation of solid tumors.

Antitumor activity was graded as −, 0 ~ 24; ±, 25 ~ 50; +, 51 ~ 100; ++ 100 ~ 200; +++, 201 or more in ascites tumors, −, 0 ~ 25, ±, 26 ~ 50, +, 51 ~ 75; ++, 76 ~ 95; +++, 96 ~ 100 (%) reduction in solid tumors

Arakawa tested ACNU for its activity against lymphoid leukemia L-1210 in BDF_1 mice [31] and reported that it was highly effective following either parenteral or oral administration [1, 32]. ACNU was also shown to be effective, against myeloid leukemia C1498 (C57BL/6), plasmacytoma X5563 (C3H/He), Ehrlich ascites carcinoma (ICR/JCL), mammary tumor MM 102 (C3H/He), and mammary tumor FM3A43 (C3H/He) of mice as well as against ascites hepatic carcinomas AH 130, AH 13, and AH 44 of rats (Donryu) [12, 32]. In addition to these leukemias and ascites tumors, ACNU has been shown to be highly effective against solid plasmacytoma X5563 (C3H/He), Ehrlich carcinoma (ICR/JCL) and meningeal sarcoma MS147 (BDF_1) of mice as well as against Sato lung carcinoma of rat [28, 32]. On the other hand, it is not particularly effective against sarcoma 37 (BDF) or adenocarcinoma 755 (BDF_1) [32].

2. *Phase I Study of ACNU* [5]

The phase I study of ACNU was conducted in 1974, with participation by 20 hospitals in Japan. Subjective side effects such as general fatigue, nausea, vomiting, and anorexia appeared 1–6 h after administration in about a third of the patients who received more than 101.8 mg ACNU/m^2 as a single dose. However, these side effects were transient and most of them required no special treatment and disappeared within 24 h after administration of the drug [5]. ACNU caused delayed myelosuppression on the hematopoietic organs. Leukopenia (less than 4000/mm^3) appeared in the 4th or 5th week after administration, with the nadir occurring after the 5th week [5, 27]. On the other hand, thrombocytopenia (less than 7×10^4/mm^3) developed in the 3rd or 4th week, and its nadir was noted 4 weeks after the drug was given [5, 27]. These hematological side effects of ACNU would be the dose-limiting factors in its application. Almost no abnormal findings were noted in blood chemistry or renal function after ACNU administration except for slight increases of SGOT and SGPT observed in less than 5% of the patients. No side effects were observed in the central and peripheral nervous, circulatory, or respiratory systems.

On the basis of the results of the phase I study, it can be concluded that the maximum clinically tolerable dose of ACNU would be 101.8–135.7 mg/m^2 at a time, that the total acceptable dose would be 300–600 mg and that the desirable interval between doses would be 6–8 weeks.

3. *Clinical Efficacy of ACNU*

Table 2 summarizes the clinical efficacy of ACNU as a single agent in 390 evaluable patients with tumors of various organs, as reported to date in Japan. In these studies, ACNU was administered in doses of more than 67.9 mg/m^2 at a time, and the total dose for each patient was more than 100 mg. In the case of solid tumors, a responder was defined as a patient in whom all the clinical evidence of an active tumor had disappeared (complete response: CR) or in whom there was a reduction of more than 50% of the sum of the products of the perpendicular diameters of a measurable lesion (partial response: PR) lasting for at least 4 weeks in the absence of a significant increase in any one lesion or the appearance of a new lesion. The therapeutic efficacy of ACNU against leukemia and myeloma was based on the standard evaluation criteria proposed by the World Health Organization (WHO). ACNU produced an overall response rate of 20.3% in the 390 cases. The response rates for patients with various organs are listed in Table 2.

The response was first observed between 1 and 3 weeks after the initiation of treatment with ACNU (within 1 week in half the patients). The duration of the response varied from patient to patient, ranging from 2 to 34 weeks [27].

Table 2. Summary of activity of ACNU alone in various tumors

Tumor type	No. of responders[a]/ no. of evaluable patients (%)		References
Lung cancer	23/115	(20.2)	8, 13, 17, 18, 21, 25, 27, 29, 33
Squamous-cell carcinoma	5/28	(17.9)	
Adenocarcinoma + large-cell carcinoma	3/36	(8.3)	
Small-cell carcinoma	14/30	(46.7)	
Unknown	1/21	(4.8)	
Carcinoma of digestive organs	11/93	(11.8)	2, 13, 14, 17, 18, 21, 25, 29, 33
Gastric cancer	6/50	(12.0)	
Colorectal cancer	2/21	(9.5)	
Malignancy of liver, pancreas, biliary tract	3/22	(13.6)	
Head and neck cancer	3/7	(42.9)	13, 27, 33
Uterine cancer	3/14	(21.4)	10, 13, 29
Other carcinomas	2/38	(5.3)	10, 13, 17, 18, 25, 27, 29, 33
Brain tumor	21/50	(42.0)	11, 19, 30
Hodgkin's disease	4/5	(80.0)	20, 25, 29
Lymphosarcoma, reticulosarcoma	4/34	(11.8)	13, 17, 20, 25, 29, 35
AML	0/8	(0)	23, 35
CML	6/10	(60.0)	35
Myeloma	0/8	(0)	16, 29, 35
Sarcomas	2/8	(25.0)	17, 27, 29
Total	79/390	(20.3)	

[a] Responders: CR + PR

The data in Table 2 suggest that ACNU seems to be effective against small cell carcinoma of the lung, brain tumors, Hodgkin's disease, and CML. More cases will be required, however, before conclusions can be drawn on its effect against other types of carcinoma and sarcoma.

4. Efficacy of ACNU Against Small-cell Carcinoma of the Lung with Regard to the Suppression of Brain Metastasis and Prolongation of Survival

Because ACNU had been shown to be active against small-cell carcinoma of the lung and remarkably effective against L-1210 cells inoculated into the brain of experimental animals [15], we carried out a comparative and retrospective study on the effect of ACNU in suppressing brain metastases as well as in prolonging survival in small-cell carcinoma of the lung. All 53 patients included in this study had small-cell carcinoma of the lung. They had been hospitalized in the National Cancer Center Hospital from December 1974 to March 1979. They were divided into two groups, 30 treated with ACNU and 23 without ACNU treatment. The chemotherapeutic regimens consisted mainly of two therapeutic arms, of (1) ACNU plus vincristine (VCR) plus dextran sulfate and urokinase, and (2) mitomycin C plus dextran sulfate and urokinase (MDU). Dextran sulfate and urokinase were used as lysosome labilizers [24].

In 30 patients treated with ACNU, ACNU was administered in a dose of 101.8 mg/m^2 at an interval of 6–8 weeks, while VCR was administered in a dose of 0.7–1.4 mg/m^2 every week (3.5 mg/m^2 for a course). The 16 responders received two courses of ACNU + VCR, while 14 nonresponders received one course of another chemotherapeutic regimen (MDU).

Of the 23 patients treated without ACNU, 21 received the MDU treatment. In the MDU arm, 6.8 mg mitomycin C/m^2 was administered intravenously once a week for more than 3 weeks at intervals of 4–6 weeks. The eight responders out of 21 patients treated with MDU received two courses of this regimen. One of the other two patients received treatment with 678.6 mg cyclophosphamide/m^2 once a week for 3 weeks along with 0.7 mg VCR/m^2 per week, and the other received 27.1 mg adriamycin (ADM)/m^2 on two successive days in two courses 3 weeks apart, along with 0.7 mg VCR/m^2 week. These two patients showed no response to either chemotherapy.

All 53 patients received 3,000 mg dextran sulfate and 18,000 U urokinase intravenously just after the administration of anticancer agents.

After completion of the chemotherapy, 20 patients (6 responders and all of 14 nonresponders) of the 30 treated with ACNU and 18 (3 responders and all of 15 nonresponders) of the 23 patients treated without ACNU received radiation therapy consisting of 5,000 rads in 25 fractions over 5 weeks to their primary lung lesion, including hilar and mediastinal lymph nodes.

Table 3. Characteristics of patients with small cell carcinoma of the lung, and their response to therapy with and without ACNU

		A. ACNU (+)	B. ACNU (−)	*P* value	
No. of patients			30	23	
Age			61.4 ± 1.1	62.6 ± 1.7	N.S.
Sex	Male		24	18	N.S.
	Female		6	5	
Stage	$IIIM_0$		17	12	N.S.
	$IIIM_1$		13	11	
Effect	Responders[b] (CR + PR)		16	8	N.S.
	Nonresponders (NR)		14	15	($P < 0.1$)
Therapeutic regimen[a]	Chemotherapy + radiation		20	18	N.S.
	Chemotherapy alone		10	5	

[a] Therapeutic regimens included ACNU in group A, and excluded it in group B
[b] Responders: CR + PR

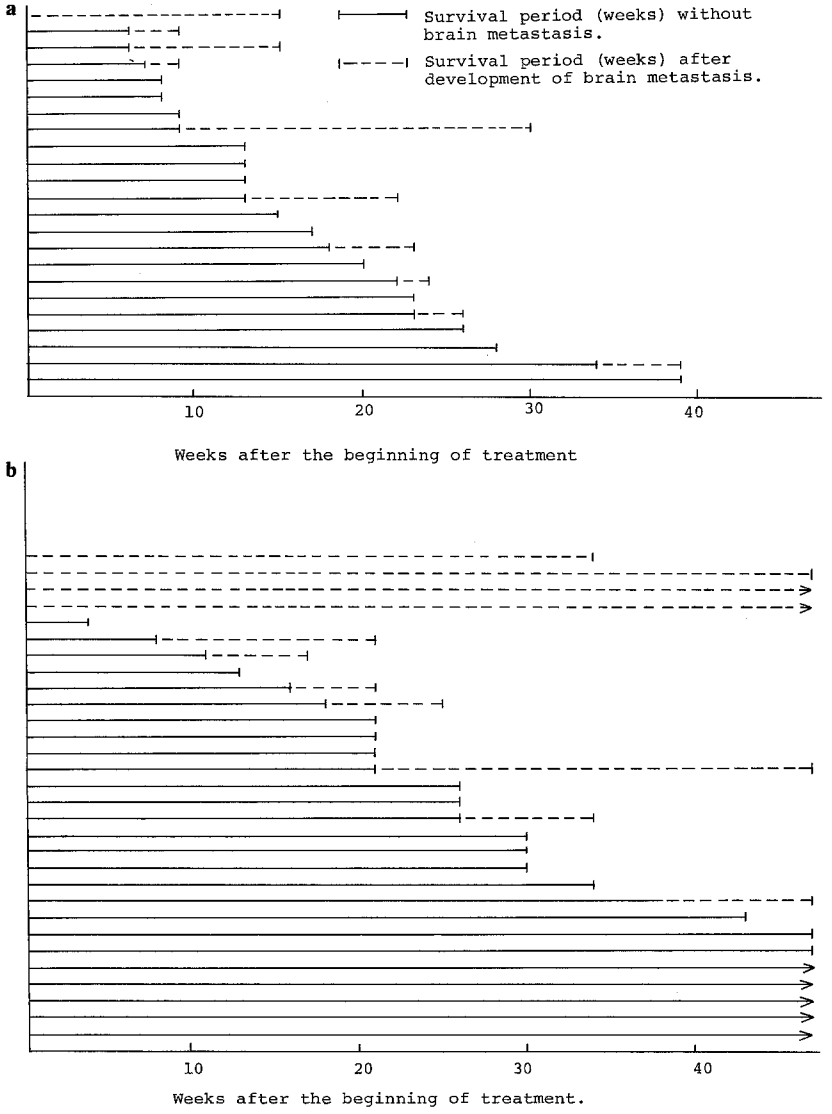

Fig. 2. a and **b** Survival of small-cell carcinoma patients with or without brain metastasis from the beginning of treatment. **a** Therapeutic regimens did not include ACNU; **b** Therapeutic regimens included ACNU

Table 3 shows the comparison of the two groups in terms of age, sex, stage of disease, therapeutic effect, and method of treatment. The response rate (CR + PR) to chemotherapy was slightly but not significantly higher in the group treated with ACNU ($P < 0.1$). No appreciable difference was found between the two groups with regard to the method of treatment, as the combined treatment of chemotherapy and radiation therapy for the primary site and metastatic lymph node were applied to 66.7% (20/30) of the group with ACNU and to 78.3% (18/23) of the group without ACNU.

Fig. 2 is a figurative representation of the length of survival (in weeks) of each patient after the beginning of treatment, in which the *solid line* represents the survival time without brain metastasis, while the *broken line* represents the survival time after development of brain metastasis. Brain metastasis had already been detected in five patients before initiating the therapy (four in the group with ACNU and one in the group without ACNU).

Table 4 indicates the frequency of brain metastasis in the two groups. The five patients in whom brain metastasis had already been detected before therapy was initiated were excluded from this analysis. The observation periods for the frequency of brain metastasis in both groups were 47 weeks from the beginning of treatment. The predicted values of brain metastasis in both groups were calculated on the basis of the data in Fig. 2 by the log-rank method [26]. The actual numbers of patients with brain metastasis were compared with the predicted values, and the difference in the frequency of brain metastasis between two groups was evaluated statistically by the χ^2-test. The frequency of brain metastasis in the 26 patients treated with ACNU was significantly lower than that of 22 patients treated without ACNU.

The survival rates of all patients in the groups were calculated according to the life-table method [6] and are shown in Fig. 3. The median survivals were 35 and 18 weeks in patients treated with and without ACNU, respectively. The difference in survival rates between two groups was evaluated by the Wilcoxon-Gehan test [9]. The survival of 30 patients treated with ACNU was significantly longer than that of 23 patients without ACNU ($P < 0.05$). Therefore, it can be concluded that ACNU reduced the rate of brain metastasis and prolonged survival in patients with small-cell carcinoma of the lung.

These data represent the comparative and retrospective evaluation of the effects of the therapy with and without ACNU on small-cell carcinoma of the lung. We have recently initiated a prospective randomized control trial with two therapeutic arms, VCR + ACNU and VCR + ADM, against small-cell carcinoma of the lung. It is hoped that active comparative chemotherapy of small-cell carcinoma of the lung might further improve the efficacy of the treatments with regard to the survival of cancer patients in the future.

Table 4. Incidence of brain metastasis

	Number of cases	Number with brain metastasis	Predicted value[a]
ACNU +	26	7	10.77
ACNU −	22	9	5.23
P value[b]		$P < 0.05$	

[a] The predicted values of brain metastases in each group was calculated on the basis of the data in Fig. 2 by the log-rank method [26]

[b] The difference in the frequency of brain metastasis between the two groups was evaluated statistically by the χ^2-test

5. Conclusion

In the comparison between ACNU and other nitrosourea derivatives such as BCNU, CCNU, and methyl-CCNU, it has been demonstrated that there is hardly any differences among them in their anticancer effects, their myelosuppressive effects, or their clinical side effects [34,

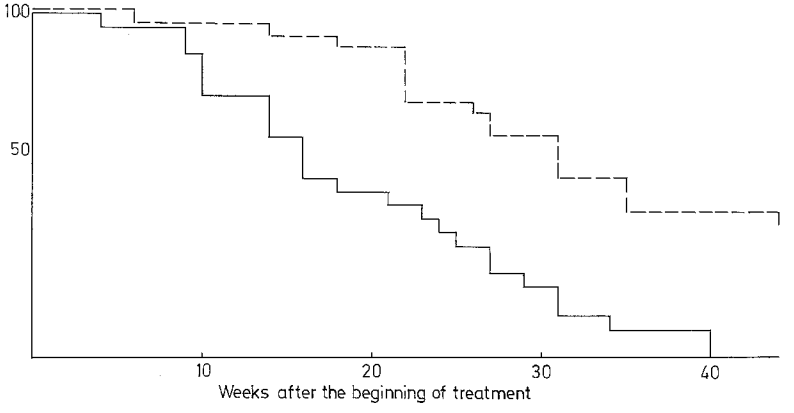

Fig. 3. Comparison of the survival of patients with small-cell carcinoma of the lung treated with ACNU (group A: – –; median 35 weeks) and without ACNU (group B: ——; median 18 weeks). $P < 0.05$ (Wilcoxon-Gehan test) [9]

36]. However, as ACNU is water-soluble and can easily be administered intravenously, it might be possible to attain precise blood levels. Despite its solubility in water, it is also soluble in lipid, and can therefore pass through the blood-brain barrier to exert its effect on brain tumors [15]. When administered as a single agent in small-cell carcinoma of the lung, ACNU was demonstrated to be highly effective in reducing the size of tumors, and also to be effective in more than 20% of the cases with head and neck carcinoma, uterine carcinoma, sarcoma, Hodgkin's disease, and chronic myelocytic leukemia. Therefore, it can be predicted that the results of treatment of carcinoma would be even more improved with active use of ACNU in combination chemotherapy against tumors that might respond to the treatment [7]. There are not yet enough results of combination chemotherapy with ACNU, and the results available have not yet been sufficiently accumulated for evaluation [37]. Most of these combination chemotherapies are based on combinations of anticancer agents with different reaction mechanisms, and it is of great interest that the delayed myelotoxicity that was regarded as the disadvantage of nitrosoureas can conversely be exploited for these combination chemotherapies. In other words, it may be possible that nitrosourea derivatives, when combined with anticancer antibiotics and alkylating agents, both of which show early myelosuppression, or when combined with bleomycin or metabolic antagonists, which have less myelotoxicity, would make each of these agents available for treatment in the full dose in combination chemotherapy. Each of the anticancer agents used for combination chemotherapy should be active as a single agent against the objective tumor. Therefore, the difference in effect between the therapies with ACNU and those without ACNU should be investigated. Randomized trials of combination chemotherapy including ACNU, taking the above-mentioned points into consideration, are underway in Japan.

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