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MITOMYCIN C IN THE TREATMENT OF CHRONIC MYELOGENOUS LEUKEMIA

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SUMMARY

Studies made of the treatment with 66 courses of mitomycin C in 28 patients with chronic myelogenous leukemia are reported. The effect of mitomycin C was investigated according to the relation between drug and host factors, comparison with the effects of other agents, and drug resistance.

Patients with less hematological and clinical symptoms responded better to mitomycin C therapy.

The remission rate of cases treated intravenously with mitomycin C was 93.8% and of cases treated orally with mitomycin C was 72.0%. The remission rate of the total cases (intravenous and oral) treated with mitomycin C was 77.3%.

The therapeutic effect of mitomycin C is considered to be equal or be somewhat superior to the effect of busulfan as a result of data on the occurrence of resistance, cross resistance, development of acute blastic crisis and life span.

Busulfan was effective in patients resistant to mitomycin C, and mitomycin C did not clinically show cross resistance to alkylating agents. Two patients resistant to mitomycin C recovered the sensitivity to mitomycin C after treatment with busulfan or 6-mercaptopurine.

Side effects were observed in 39.4% of 66 cases, but severe side effect causing suspension of mitomycin C was rare.

I. INTRODUCTION

Human leukemia serves as a useful investigative model in which the definite effect of anti-cancer agents can be evaluated quantitatively by factors such as the improvement of hematological findings and clinical symptoms, the remission rate, and the prologation of life span.

In chronic myelogenous leukemia the alkylating agents, busulfan[1)-15)], TEM [15)-23)], thio-TEPA[12)15)24)-27)], nitromin[15)23)28)-31)], have been used for treatment of the disease. 6-mercaptopurine, one of the anti-metabolites, has also been found effective[32)-35)].

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Recently, following the discovery of mitomycin C[36)-38)], this new antibiotic has been tried for the treatment of chronic myelogenous leukemia, and the effects of the drug have been reported by Kimura[39)40)], Hibino[41)42)], Kurita[43)44)], Ota[45)], Yamada[46)], and this author[47)48)]. The patients with chronic myelogenous leukemia were treated at the First Department of Internal Medicine of the Nagoya University School of Medicine over the past 10 years. Among them, 28 patients (total 66 cases of treatment courses) have been under mitomycin C therapy.

This paper deals with the analysis of hematological and clinical findings in relation to the effect of mitomycin C, and comparison of the effect of mitomycin C with other agents as regards the remission rate, duration of remission, and life span. The occurrence of acute blastic crisis, the emergence of the clinical resistance to mitomycin C, and the cross resistance to other drugs, which alters greatly the prognosis of the patients, have also been studied.

II. MATERIALS AND METHODS

Mitomycin C was obtained from Kyowa Hakko Co. Ltd. An ampule with 2 mg of mitomycin C was dissolved in 20 ml of 5% glucose or in 20 ml of physiological saline.

The initial dosage of 1-2 mg was injected intravenously once a day. In case of oral use, 5-6 mg tablets were administered one to three times daily. When the decrease of white blood cell count could not be observed after 2 weeks of initial therapy, the subsequent oral dosage was increased to 9 mg a day.

The evaluation of the response of the patients to the drug was carried out by a scoring system following Kimura's criteria (Table 1)[40)49)50)].

Patients obtained points of 40 or more were classified as remission case (complete remission, 60 points or more; partial remission, 59-40 points), and less than 39 points were evaluated as cases of failure of the treatment.

The clinical and hematological data prior to the first course of mitomycin

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Abbreviation of agents

Busulfan	Myleran, Dimethane sulphonyloxybutane
Endoxan	Cytoxan, Cyclophosphamide
Nitromin	Nitrogen mustard *N*-oxide
6 MP	6-mercaptopurine
RC-4	*P*-phenylenediphosphoric acid tetraethyleneimide
AL-NM	Alanine nitrogen mustard
MMC	Mitomycin C
TEM	Triethylene melamine
Thio-TEPA	Triethylene thiophosphoramide
Trenimon	Triethylene benzoquinone
N. M.	Nitrogen mustard

TABLE 1. Criteria for Evalution of Response to Chemotherapy in Chronic Leukemia

	Grade I	Score	Grade II	Score	Grade III	Score
A. Bone marrow	1. Immature cells decrease and leukopoiesis becomes normal	10	1. Immature cells decrease	5	No improvement or improvement less than A-Grade II	0
	2. Erythropoiesis increases to more than 20%	10	2. Erythropoiesis increases, but less than20%	5		
B. Peripheral blood	1. WBC decrease to less than 15,000	20	1. WBC decrease, but not to less than 15,000	10	No improvement or improvement less than B-Grade II	0
	2. Immature cells disappear or decrease to less than 10%	10	2. Immature cells decrease to less than 20%	5		
	3. Hgb contents increase to more than 80%	10	3. Hgb contents increase to more than 60%	5		
	4. Platelet counts do not decrease to less than 150,000	10	4. Platelet counts do not decrease to less than 80,000	5		
C. Physical findings	Splenomegaly disappears or decreases to less than 1/3 in size, marked decrease of hepatomegaly and lymphadenopathy	20	Spleen decreases, but not to less than 1/3 in size, significant reduction of hepatomegaly and lymphadenopathy	10	No improvement or improvement less than C-Grade II	0
D. Clinical findings	Asymptomatic, or marked improvement of leukemic symptoms	10	Definite improvement, though still symptomatic	5	No improvement or improvement less than D-Grade II	0

Complete remission: over 60 points
Partial remission: from 40 to 59 points

TABLE 2. Clinical and Hematological Findings, and Effects of Mitomycin C in the Patients with Chronic Myelogenous Leukemia

Case	Age	Sex	Clinical and Hematological Findings Before MMC Therapy								Effect of Mitomycin C Therapy					
			WBC	Hgb	PL	Immature Leukocyte	Mbl (Peripheral Blood)	Mbl (Bone Marrow)	Splenomegaly	Hepatomegaly	Lymphadenopathy	Daily Dose	Dose required to give Remission	Days required to give Remission	Duration of Remission	Effect	Survival Time
				%	$\times 10^4$	%	%	%				(mg)	(mg)		(month)	**	(month)
I.G.	38	M	84,600	91	18.6	6.5	0	0.2	−	+	−	2-3	37	15	0.5	PR	46
A.W.	61	F	72,600	65		25.5	0	0	++	−	−	1	26	26	6	CR	62
K.A.	49	F	72,800	79		10.0	0	0	+	−	−	0.5-1	28	28	5	CR	24
T.N.	22	M	110,600	85	14.0	23.0	0	0.4	+	−	−	0.5-2	71	39	8	CR	49
T.I.	34	M	95,400	97	10.3	26.0	0	2.2	+	−	−	1	13	13	5	CR	69
K.T.	28	M	31,400	68	19.5	66.0	5.5	6.6	++	++	−	1-2	—	—	—	NE	23
K.O.	34	F	265,800	78	16.3	19.5	0		++	−	−	1	70	70	3	CR	46
S.S.	30	F	153,200	54	28.2	28.0	0	0.9	++	−	+	1-2	61	61	14	CR	56
K.M.	24	M	90,600	87		42.0	0	0	+	−	−	5*	70	14	1.5	CR	56
K.W.	36	F	77,400	51					++	−	−	5*	—	—	—	NE	46
K.S.	34	M	70,000	76	28.4		0		++	−	−	5*	—	—	—	NE	43
M.K.	44	F	54,000	62	49.8	21.0	0		++	++	−	5*	85	17	7.5	CR	19
T.S.	34	M	66,800	60	56.8	25.5	0.5	3.4	+	++	+	5*	70	14	2.5	CR	17†
Y.K.	30	F	144,000	49	5.8	18.0	0.5	2.2	++	++	+	5*	—	—	—	NE	3
G.N.	55	M	299,200	53	21.8	38.0	1.0	2.4	++	+	−	5*	105	38	3	CR	18
M.T.	19	F	185,000	57	152.5	27.5	0	1.3	++	++	−	5*	75	15	11	CR	44†
S.S.	19	M	380,000	65	14.1	25.5	1.0	1.2	++	++	−	5*	220	44	2	CR	42†
Z.Y.	67	M	199,600	25	10.3		1.0		−	+	−	5*	210	42	13	CR	23
T.O.	23	M	313,700	56	29.7	36.5	0.5	1.6	++	++	+	5*	—	—	—	NE	30†
S.O.	46	M	70,600	80	19.6	36.5	0.5		++	−	−	5-7.5*	450	86	9.5	CR	37†
K.O.	38	M	42,800	85	82.5	19.0	0.5	1.6	−	−	−	4*	16	4	0.5	CR	12
S.S.	47	M	46,000	80	91.7	39.0	2.0	0.4	+	++	−	4-6*	168	28	3	CR	23†
F.I.	36	F	353,000	64	40.8	58.5	3.0	0	++	++	−	6*	—	—	—	NE	18†
T.S.	22	M	553,000	46	33.5	60.0	3.0	3.2	++	++	++	6-9*	—	—	—	NE	22†
T.M.	42	M	105,200	38	39.1	46.0	0	1.2	+	++	+	6-9*	—	—	—	NE	12†
T.S.	42	F	272,000	37	22.8	58.0	1.0	0.8	++	++	−	4-6*	114	19	2	CR	19†
T.U.	35	M	318,000	54	16.9	12.0	0	0.4	++	++	−	6-9*	—	—	—	NE	11†
N.S.	38	M	150,000	80	40.8	37.0	0	1.4	++	++	−	5-7.5*	323	56	5.5	CR	11

**CR: Complete Remission PR: Partial Remission NE: No Effect *Oral administration †Alive

C treatment, the effect of the therapy, and the life span of the 28 patients are shown in Table 2.

III. RESULTS

1) Relation of hematological findings and clinical symptoms to the effect of mitomycin C.

The first course as well as the repeated course of mitomycin C treatment were included in this study. The factors influencing the effect of mitomycin C such as hematological findings and clinical symptoms prior to mitomycin C therapy were investigated.

Duration of remission which was measured from the day of remission to the day of relapse, days and dose required to achieve remission were expressed by median value.

a) White blood cell count

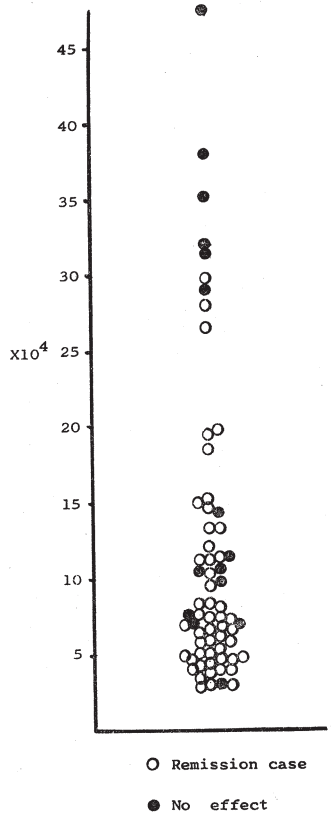


FIG. 1.
Relation of WBC to remission.

TABLE 3. Relation of Peripheral W B C to Remission

	W B C prior to MMC Treatment	
	Less than 10^5	10^5 or more
No. of Cases	40	26
Remission Case	35	16
Remission Rate	87.5 %	61.6 %
Duration of Remission	4.3 months	3.5 months
Days required until Remission	15.0 days	36.3 days
Dose required until Remission	48.4 mg	101.5 mg

As shown in Fig. 1, white blood cell count (WBC) of the patients prior to mitomycin C treatment ranged between 30,000 and 500,000 per cu. mm. The cases were divided into two groups by whether the WBC was less than 10^5 or 10^5 or more (Table 3).

The remission rate of the group with WBC less than 10^5 was 87.5% and was significantly higher ($P<0.05$ by Chi square test) than 61.6% of the group with WBC of 10^5 or more. The duration of remission for the group with less than 10^5 was 4.3 months and that with 10^5 or more was 3.5 months. This difference between the two groups was statistically insignificant.

The days and the dose required to achieve remission for the group of less than 10^5 was 15.0 days and 48.4 mg, respectively. The data for the group with 10^5 or more was 36.3 days and 101.5 mg. The values of the former were one half of the latter and were significantly shorter and smaller ($P<0.01$ by T test).

b) Percent of immature leukocyte in peripheral blood

The percentage of immature leukocyte (myeloblast, promyelocyte, myelocyte, and metamyelocyte) in the patients before mitomycin C treatment is shown in Fig. 2. The percentage spread was between 4.5% and 66.0%.

As shown in Table 4, the patients were divided into the following four

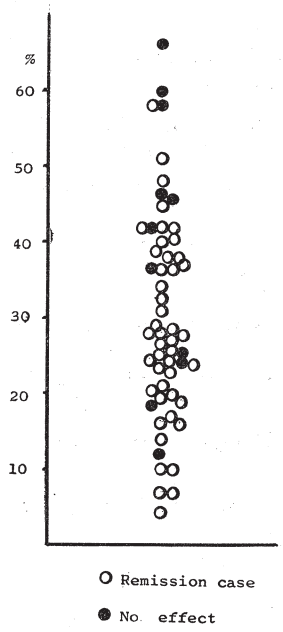


FIG. 2.
Relation of immature leukocyte per cent in peripheral blood to remission.

TABLE 4. Relation of Immature Leukocyte per cent in Peripheral Blood to Remission

	Immature Leukocyte % prior to MMC Treatment			
	Less than 20%	20–29%	30–39%	40% or more
No. of Cases	14	17	13	13
Remission Case	12	15	12	7
Remission Rate	85.7 %	88.2 %	92.3 %	53.8 %
Duration of Remission	3.5*	5.2*	3.0*	2.5*
Days required until Remission	22.5	13.8	25.0	10.8
Dose required until Remission	45.0 mg	61.3 mg	100.0 mg	65.0 mg

* months

groups: less than 20%, 20-29%, 30-39%, and 40% or more. The remission rates, 85.7%, 88.2%, and 92.3%, were similar in the 3 groups of less than 39% of immature leukocyte, but the rate, 53.8%, in the group of 40% or more was significantly lower ($P<0.05$). No statistical significance was observed between each groups for the duration of remission, the days, and the dose required to achieve remission.

c) *Appearance of myeloblast in peripheral blood*

The percent of myeloblast in a smear of peripheral blood prior to the mitomycin C treatment is shown in Fig. 3. The extreme was 5.5%.

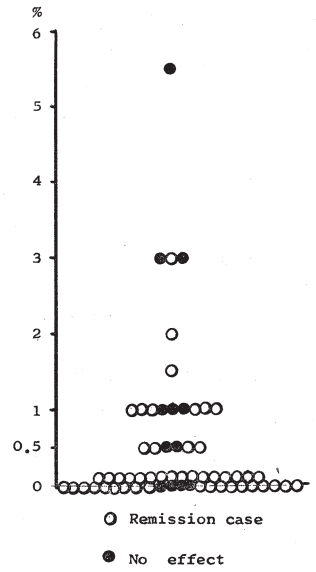


FIG. 3.
Relation of myeloblast per cent in peripheral blood to remission.

TABLE 5. Relation of Myeloblast per cent in Peripheral Blood to Remission

	Myeloblast % prior to MMC Treatment	
	Myeloblast (−)	Myeloblast(+) (more than 0.5%)
No. of Cases	39	21
Remission Case	35	13
Remission Rate	89.5 %	61.9 %
Duration of Remission	4.5 months	2.6 months
Days required until Remission	15.0 days	30.0 days
Dose required until Remission	48.8 mg	120.0 mg

The patients were divided into two groups, namely, one with myeloblast in the peripheral blood and the other without myeloblast. The patients with acute blastic crisis were excluded from this study. As shown in Table 5, the remission rate, 89.5% for the group without myeloblast was significantly higher than the 61.9% for the group with myeloblast ($P<0.05$). The days and the dose required until remission for the former group was 15.0 days and 48.8 mg, respectively, and 30 days and 120.0 mg for the latter group. The data of the former group were about one half of the latter ($P<0.02$). However, in the duration of remission no significant difference was observed between the two groups.

d) Percent of myeloblast in bone marrow

The distribution of the percent of myeloblast in 39 patients who received bone marrow biopsy prior to the treatment is shown in Fig. 4. The patients with acute blastic crisis were excluded. The maximum was 6.5%.

Two groups, of one with myeloblast less than 1% and the other 1% or more were studied. The remission rate, 90.0%, for the former group was

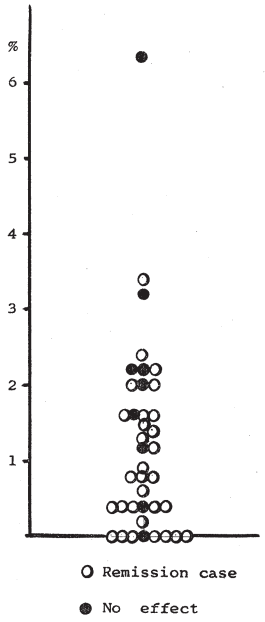


FIG. 4.
Relation of myeloblast per cent in bone marrow to remission.

TABLE 6. Relation of Myeloblast per cent in Bone Marrow to Remission

	Myeloblast % prior to MMC Treatment	
	Less than 1 %	1 % or more
No. of Cases	20	19
Remission Case	18	12
Remission Rate	90.0%	63.2 %
Duration of Remission	4.2 months	3.3 months
Days required until Remission	26 days	20 days
Dose required until Remission	50.0 mg	75.0 mg

significantly higher than the 63.2% for the latter group ($P<0.05$). In the duration of remission no significant difference was observed between the two groups ($P>0.05$). (Table 6)

e) Hemoglobin percent

The hemoglobin percent of the patients prior to therapy is shown in Fig. 5, and ranged between 25% and 113%.

Two groups in which one had hemoglobin of 80% or more and the other less than 80% were studied. The remission rate for the group of 80% or more was 100%. The rate for the group of less than 80% was markedly lowered to 62.5% ($P<0.01$). No significant difference was observed in the duration of remission, the days, and the dose between the two groups ($P>0.05$).

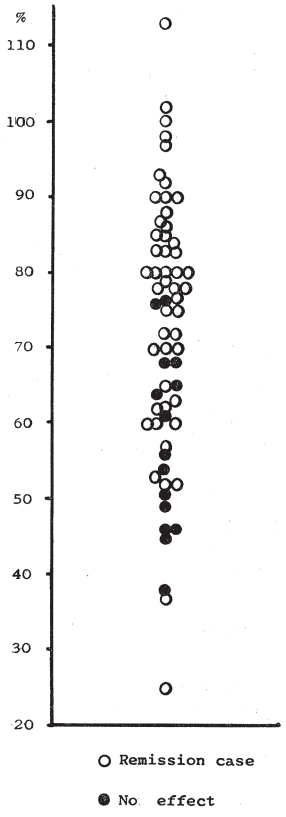


FIG. 5.
Relation of hemoglobin per cent to remission.

TABLE 7. Relation of Hemoglobin per cent to Remission

	Hemoglobin % prior to MMC Treatment	
	80 % or more	Less than 80 %
No. of Cases	24	40
Remission Case	24	25
Remission Rate	100 %	62.5 %
Duration of Remission	3.5 months	4.3 months
Days required until Remission	13.1 days	20.0 days
Dose required until Remission	46.6 mg	65.8 mg

TABLE 8. Relation of Platelet Count to Remission

	PL Count prior to MMC Treatment	
	Less than 2×10^5	2×10^5 or more
No. of Cases	22	38
Remission Case	17	29
Remission Rate	77.3 %	76.3 %
Duration of Remission	4.8 months	2.7 months
Days required until Remission	14.5 days	20.6 days
Dose required until Remission	55 mg	75 mg

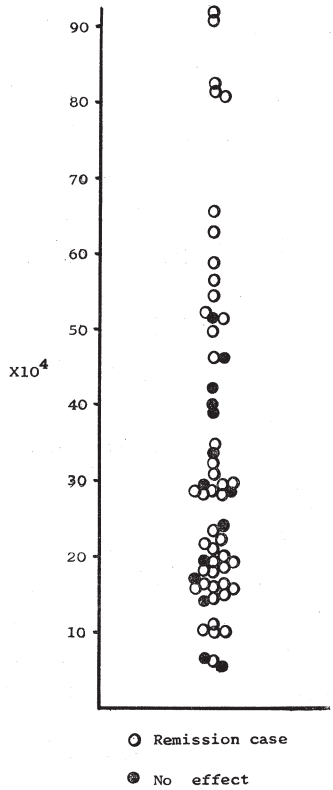


FIG. 6.
Relation of platelet count to remission.

f) Platelet count

The platelet count of the patients priort to treatment spread from 30,000 to 920,000 per cu. mm (Fig. 6). The patients were studied in two groups in which the platelet count was less than 2×10^5 and 2×10^5 or more. Between the two groups, no statistical significances were observed in the rate of remission, the duration of remission, the days, and the dose required to achieve remission (Table 8).

g) Splenomegaly

The study was made in two groups, one with splenomegaly of less than 3 fb (in size below costal margin) and the other 3 fb or more. The remission rate of the group with less than 3 fb of splenomegaly was 90.0% and was significantly higher than the 50.0% of the latter ($P<0.01$). However, no significant differences were noted between the two groups in the duration of remission, and the days and the dose until remission (Table 9).

TABLE 9. Relation of Splenomegaly to Remission

	Splenomegaly prior to MMC Treatment	
	Less than 3 fb	3 fb or more
No. of Cases	44	22
Remission Case	40	11
Remission Rate	90.0 %	50.0 %
Duration of Remission	3.7 months	5.3 months
Days required until Remission	16.3 days	25.0 days
Dose required until Remission	61.2 mg	90.0 mg

h) Hepatomegaly

Groups with and without hepatomegaly were investigated. The remission rate of the group without hepatomegaly was 90.0% and was significantly higher than the 65.7% with hepatomegaly ($P<0.05$). Other results indicated no significant differences between the two groups (Table 10).

i) Lymphadenopathy

The patients with superficial lymphnodes of the size of more than a small finger tip were considered to have lymphadenopathy. As shown in Table 11, patients with lymphadenopathy were only 9 out of 65 cases. The remission

TABLE 10. Relation of Hepatomegaly to Remission

	Hepatomegaly prior to MMC Treatment	
	(−)	(+)
No. of Cases	30	35
Remission Case	27	23
Remission Rate	90.0 %	65.7 %
Duration of Remission	4.5 months	2.5 months
Days required until Remission	14.7 days	24.4 days
Dose required until Remission	57.5 mg	75.0 mg

TABLE 11. Relation of Lymphadenopathy to Remission

	Lymphadenopathy prior to MMC Treatment	
	(−)	(+)
No. of Cases	56	9
Remission Case	47	3
Remission Rate	84.0 %	33.3 %
Duration of Remission	4.0 months	2.0 months
Days required until Remission	17.5 days	22.5 days
Dose required until Remission	64.2 mg	70.0 mg

rate of the patients without lymphadenopathy was 84.0% and was markedly higher than the 33.3% of those with lymphadenopathy ($P<0.01$).

2) Comparison of the effect of mitomycin C and other chemotherapeutic agents

This investigation was carried out on patients who were treated at the First Department of Internal Medicine of the Nagoya University School of Medicine.

a) Rate and duration of remission

The effect of various chemotherapeutic agents on the first course and the repeated course are shown in Table 12 as the number of remission cases, with the remission rate in parentheses.

TAELE 12. Effects of Various Chemotherapeutic Agents in Chronic Myelogenous Leukemia

Agent	Total	Complete Remission			Partial Remission	Remission Case
		100-80*	79-60*	Subtotal		
Mitomycin C (inj)	16	9	4	13 (81.3)	2	15 (93.8)
Mitomycin C (oral)	50	20	14	34 (68.0)	2	36 (72.0)
Subtotal	66	29	18	47 (71.2)	4	51 (77.3)
Nitromin (inj)	11	2	6	8 (72.7)	1	9 (81.8)
Nitromin (oral)	7	1	3	4 (57.1)	1	5 (71.4)
Nitromin-D	8	3	5	8 (100.)	0	8 (100.)
Subtotal	26	6	14	20 (76.9)	2	22 (84.6)
Busulfan	36	11	11	22 (61.1)	5	27 (75.0)
TEM	15	5	4	9 (60.0)	1	10 (66.7)
Thio-TEPA	13	4	1	5 (38.5)	1	6 (46.2)
Endoxan	6	0	0	0	2	2 (33.3)
RC-4	4	1	3	4 (100.)	0	4 (100.)
Trenimon	4	0	1	1 (25.0)	0	1 (25.0)
Nitrogen Mustard	5	0	1	1 (20.0)	1	2 (40.0)
Urethan	7	0	3	3 (42.9)	2	5 (71.4)
Colcemid	5	0	1	1 (20.0)	2	3 (60.0)
Carcinophillin	3	1	0	1 (33.3)	0	1 (33.3)
Chromomycin	2	0	0	0	0	0
6 MP	10	2	4	6 (60.0)	1	7 (70.0)
6 MP+MMC	4	2	0	2 (50.0)	2	4 (100.)
6 MP+Busulfan	13	1	4	5 (38.5)	4	9 (69.2)
Total	219	62	65	127 (58.0)	27	154 (70.3)

* Score.

TABLE 13. Response to Various Chemotherapies to number of Course of Treatment

	Mitomycin C		Busulfan		T E M		Nitromin	
	Total	Rem. Case	Total	Rem. Case	Total	Rem. Case	Total	Rem. Case
1 st	21*	15 (71.4%)	9	8 (88.9%)	4	4 (100%)	8	8 (100%)
2 nd	11	10 (90.9%)	7	6 (85.7%)	2	1 (50.0%)	4	3 (75.0%)
3 rd	7	7 (100%)	3	2 (66.7%)	2	1 (50.0%)	2	2 (100%)
4 th	7	6 (85.7%)	1	0			2	1 (50.0%)
5 th	3	3 (100%)					1	1

* Including 6 patients who were under the 2 nd course of treatment at the time when these data were collected.

Sixteen cases were treated intravenously with mitomycin C. The remission rate of these cases was remarkably high, being 93.8%. By the oral use of mitomycin C, the remission rate of 50 cases was 72.0%, which was relatively lower than that obtained by intravenous treatment. The remission rate of the total cases (intravenous and oral) treated with mitomycin C was 77.3%. This remission rate was similar to the 84.6% for nitromin, 75.0% for busulfan, 66.7% for TEM, and 70.0% for 6 MP. The remission rate for thio-TEPA was rather low, being 46.2%.

The results of patients treated with mitomycin C, busulfan, TEM or nitromin for the first course and then subsequently treated with the same drug are shown in Table 13. The remission rate by number of courses of treatment are indicated. In the first course with mytomycin C, the remission was 15 out of 21 cases (71.4%), in the 2 nd course 10 out of 11 cases (90.9%) and in the 3 rd course 7 out of 7 cases (100%). Decrease of the remission rate was not evident in subsequent courses. The remission in the first course with busulfan was 8 out of 9 cases (88.9%) and in the 2 nd course 6 out of 7 cases (85.7%).

The rate and duration of remission with the four drugs are shown in Table 14 and Table 15. In the first course, the duration of remission was 8.0 months for busulfan, 6.0 months for TEM, 4.5 months for mitomycin C, and

TABLE 14. Remission rate and Duration of Remission in Various Treatments (First course)

	M M C	Busulfan	T E M	Nitromin
No. of cases	21	9	4	8
Remission case	15	8	4	8
Remission rate	71.4%	88.9%	100%	100%
Duration of remission	4.5*	8.0*	6.0*	1.5*

* months.

1.5 months for nitromin (Table 14). In the subsequent course, the remission rate of mitomycin C remained at 90.9%, but the remission rates of other drugs decreased when compared with those of the first course. The duration of remission of mitomycin C therapy in the subsequent course was 4.0 months and was similar to that of the first course. However, the duration in the subsequent course for busulfan and TEM decreased to 3.0 months and 2.0 months, respectively.

TABLE 15. Remission Rate and Duration of Remission in Various Treatments (On and after the 2nd course)

	M M C	Busulfan	T E M	Nitromin
No. of Cases	33	11	4	13
Remission Case	30	7	2	10
Remission Rate	90.9%	63.6%	50.0%	76.9%
Duration of Remission	4.0*	3.0*	2.0*	1.7*

* months.

b) Acute blastic transformation

Acute blastic crisis dominates the prognosis of patients with chronic myelogenous leukemia[51)-55)]. Studies were made on expired patients treated mainly with the same agent throughout the course of the disease. Table 16 shows the number of patients who died by acute blastic crisis and the period in months expressed as the median from the beginning of chemotherapy to the sign of acute blastic crisis. The rate of crisis for mitomycin C was 61.6% and for

TABLE 16. Acute Myeloblastic Transformation in Chronic Myelogenous Leukemia Treated with Various Agents

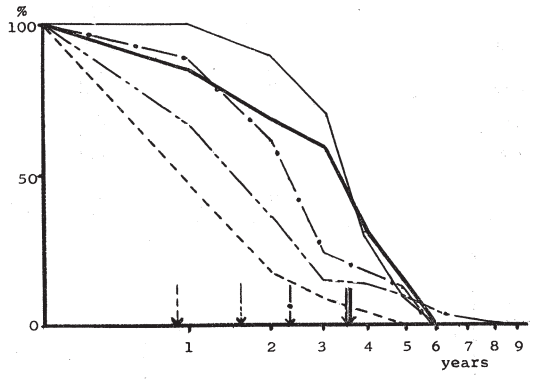
Agent	Total case	A. M. T. case	A. M. T. (%)	Months until A. M. T.
Nitromin	8	6	75.0	21.5 (13-25)
N. M. and AL.-N. M.	5	3	60.0	10.0 (4-20)
T E M	4	4	100.0	33.0 (18-56)
Busulfan	10	7	70.0	30.5 (4-40)
M M C	13	8	61.6	35.5 (7-61)
Others	16	11	68.8	18.0 (2-72)
Total	56	39	69.6	22.5 (2-72)

A. M. T. = Acute myeloblastic transformation.

busulfan 70.0%. The incidence for most drugs was more than 60.0%. In total, 39 cases out of 56 (69.6%) died of acute blastic crisis. The period from onset of chemotherapy to crisis was 21.5 months for nitromin and 10.0 months for nitrogen nustard or alanine nitrogen mustard. However, the period for busulfan, TEM, and mitomycin C ranged from 30.5 months to 35.5 months.

c) Life span

The patients who were treated mainly with the same agent throughout the disease were studied. As shown in Fig. 7, the median survival time of patients with symptomatic treatment was 0.95 years, and 1.50 years with radiation therapy. Employing chemotherapy the survival time with nitromin was 2.33 years,



Life span (years)	1	2	3	4	5	6	7	8	9	Cases	Median
Symptomatic therapy – – – – –	13	8	2	1	1					25	0.95
Radiation therapy — – – —	16	16	8	1	3	4	0	0	1	49	1.50
Nitromin — · —	1	2	3	0	1	1				8	2.33
Busulfan ———	0	1	2	4	2	1				10	3.50
Mitomycin C ———	2	2	1	4	2	2				13	3.50

FIG. 7. Survival time of chronic myelogenous leukemia.

however, the life span with mitomycin C and with busulfan was 3.50 years. The life spans with mitomycin C and with busulfan were prolonged to more than 3 times that by symtomatic treatment and more than twice that by radiation therapy.

3) Side effects

The side effects of mitomycin C in the treatment of chronic myelogenous leukemia are shown in Table 17. Various side effects were seen in 26 (39.4%) of the 66 cases. However, severe side effect causing suspension of mitomycin C therapy was rare.

Gastro-intestinal side effects were 46.4% followed by 34.6% with proteinuria. There were only 2 cases (7.8%) with edema. Proteinuria disappeared almost entirely by suspending the administration of mitomycin C.

The platelet count in most cases decreased after the administration of mitomycin C. However, the minimum platelet count after or during the therapy

TABLE 17. Side Effects in Mitomycin C Therapy

Without side effect	40	60.6 %
With side effect	26	39.4
Anorexia	8	30.8 %
Nausea	2	7.8
Diarrhea	2	7.8
Subtotal	12	46.4
Proteinuria	9	34.6
Edema	2	7.8
Hemorrhage	2	7.8
Malaise	1	3.9
Amenorrhea	2	7.8
Impotence	1	3.9
Total	29	

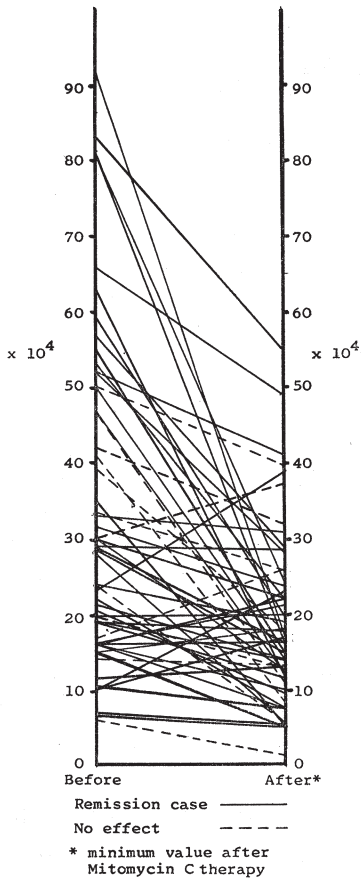


FIG. 8.
Paltelet count before and after mitomycin C therapy.

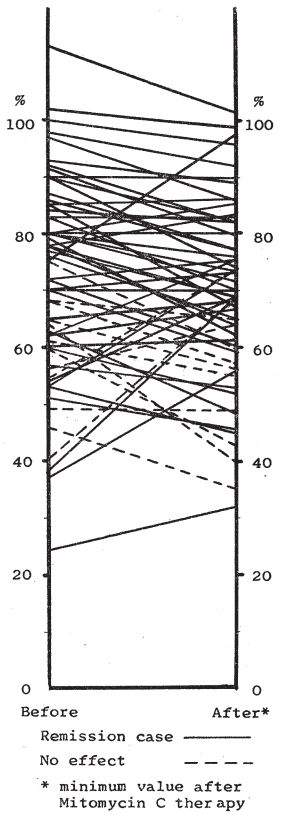


FIG. 9.
Hemoglobin per cent before and after mitomycin C therapy.

scarcely decreased below 100,000 per cu. mm (Fig. 8). In only 2 cases mitomycin C had to be suspended because of bleeding tendency.

The minimum hemoglobin values after or during mitomycin C therapy are shown in Fig. 9. Decrease of hemoglobin was not remarkable.

4) Resistance to mitomycin C and cross resistance to other agents

a) Occurrence of resistance

The occurrence of drug resistance is one of the major obstacles in the treatment of this disease. As shown in Table 18, the remission rate did not decrease following a number of courses of mitomycin C treatment. The duration of remission was 4.5 months for the first course and 4.0 months for

TABLE 18. Response to Mitomycin C Therapy to number of Course of Treatment

	Total cases	Remission case	Duration of remission	Days required until remission	Dose required until remission
1 st	21	15 (71.4%)	4.5 months	30 days	77.5 mg
2 nd	11	10 (90.9%)	4.0	15	55.0
3 rd–10th	22	20 (90.9%)	4.0	15	50.0

subsequent courses. The days and the dose to achieve remsision was shorter and smaller in subsequent courses. These data suggested that the development of resistance to mitomycin C in this disease was slow and rare. However, the emergence of resistance could not be disregarded. Patients who became resistant to mitomycin C after frequent treatments or who did not respond to the first course of treatment are described in the next paragraph.

b) Resistant cases

Case 1: (Fig. 10) A woman 30 years old. She was hospitalized for frequent diarrhea and pain in the left epigastric region. She had remissions for 14 months after the first course (2 mg of mitomycin C intravenously) and for 13 months after the second course (5 mg of mitomycin C orally). In the third course, 5 mg of mitomycin C was given orally and a remission was obtained, but the duration of remission shortened to 2 months. During the fourth course, the WBC decreased temporally by treatment with 5 mg of mitomycin C. However, the spleen did not decrease in size, and furthermore, the WBC reincreased despite of successive treatment with mitomycin C. This

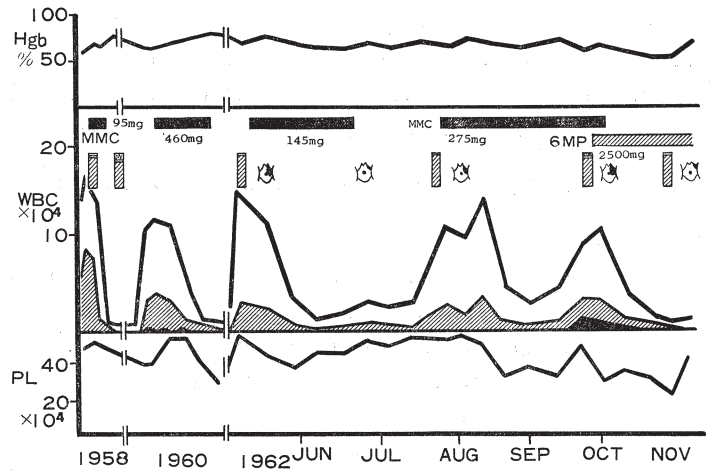


FIG. 10. Case 1. Chronic myelogenous leukemia F. Age 30.

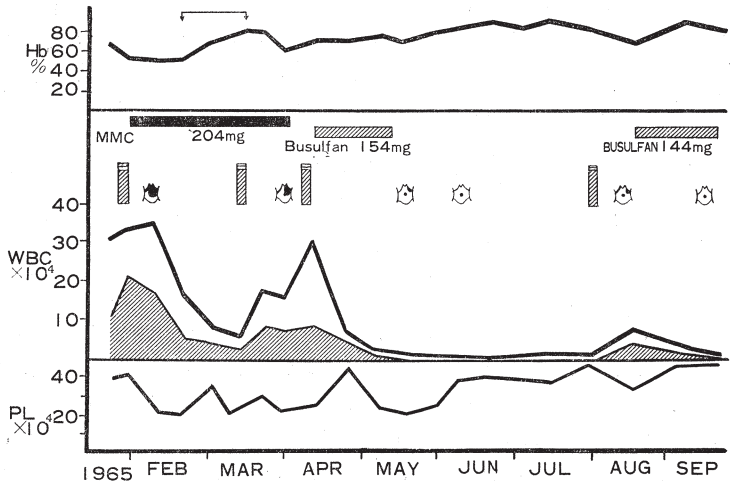


FIG. 11. Case 2. Chronic myelogenous leukemia F. Age 36.

case was considered to have become resistant to mitomycin C during the 4th course. The patient was then treated with 6 MP (100 mg daily orally), and went into remission.

Case 2: (Fig. 11) A house wife 36 years old. Her complaints were abdominal tumor and gradual anemia. She was given orally 6 mg of mitomycin C. She had a temporal decrease of WBC, but no decrease of spleen size. The WBC reincreased and she was considered to be resistant to the drug. With subsequent use of busulfan (6 mg orally daily), a remission for 3.5 months was obtained.

Case 3: (Fig. 12) A man 22 years old. His chief complaints were unin-

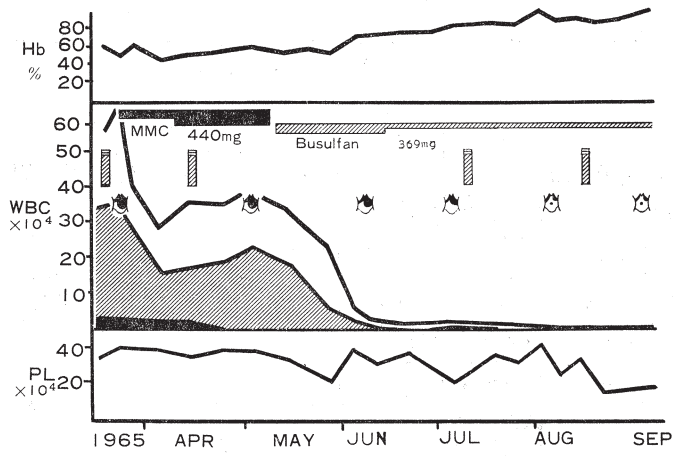


FIG. 12. Case 3. Chronic myelogenous leukemia M. Age 22.

terrupted bleeding from trauma in the right leg and an abdominal tumor. He received 6 mg of mitomycin C orally. The WBC dropped slightly, but the spleen did not diminish in size. He was then given 9 mg of mitomycin C subsequently, however, no response was observed. Later, with 6 mg of busulfan the patient reached remission for more than 8 months.

c) Cross resistance

The effect of busulfan or 6-mercaptopurine on patients who were resistant to mitomycin C was studied. Furthermore, the effect of mitomycin C on patients who were previously treated with various alkylating agents was also evaluated.

As in case 1, case 2, and case 3, the resistant patients were treated with busulfan or 6 MP as a subsequent course. So far 10 resistant cases were treated daily with 6-10 mg of busulfan (Table 19). Seven complete remissions and 2 partial remissions were obtained out of 10 cases. This remission rate, 90%, was as high as the 88.9% obtained for the first course of busulfan.

The effect of 6 MP on 6 resistant patients is shown in Table 20. Three out of 6 cases responded to 6 MP. The remission rate of these patients was lower than the rate of 70% obtained in all the cases with 6 MP.

The effect of mitomycin C on patients who had previously been treated with busulfan, nitromin, thio-TEPA, alanine nitrogen mustard, trenimon, RC-4, and endoxan, is shown in Table 21. Remissions by mitomycin C were obtained in 6 out of 8 cases (5 complete remissions and 1 partial remission). The remission rate of these patients was 75% and was similar to the rate of 71.4% obtained with the first course of mitomycin C.

The above evidence indicated that busulfan did not clinically show cross

TABLE 19. Effect of Busulfan to Mitomycin Resistant Cases of Chronic Myelogenous Leukemia

	I course	II	III	IV	V	VI	VII
1. F19	MMC	MMC	ENDOXAN	MMC	MMC	BUSULFAN	MMC
2. F34	MMC	MMC	BUSULFAN				
3. M33	ENDOXAN	MMC	6MP	BUSULFAN			
4. F36	MMC	MMC	THIO-TEPA	6MP	BUSULFAN	BUSULFAN	
5. F36	MMC	BUSULFAN	BUSULFAN				
6. M17	MMC	BUSULFAN					
7. M42	MMC	BUSULFAN					
8. M22	MMC	BUSULFAN					
9. M35	MMC	BUSULFAN					
10. M34	MMC	TRENIMON	MMC	BUSULFAN	BUSULFAN 6MP		

← 6 →6 months DURATION OF REMISSION

COMPLETE REMISSION PARTIAL REMISSION

MMC NO EFFECT

TABLE 20. Effect of 6-Mercaptopurine to Mitomycin Resistant Cases of Chronic Myelogenous Leukemia

	I course	II	III	IV	V	VI
1. F 30	MMC	MMC	MMC	MMC	6MP	
2. M46	MMC	MMC	6MP	6MP	MMC	MMC
3. M19	MMC	6MP	6MP			
4. F 36	MMC	MMC	THIO-TEPA	6MP		
5. M33	MMC	6MP				
6. M34	MMC	BUSULFAN	BUSULFAN 6MP			

← 6 →6 months DURATION OF REMISSION

COMPLETE REMISSION PARTIAL REMISSION MMC NO EFFECT

resistance to mitomycin C. Further, it might be assumed that there was no cross resistance between mitomycin C and alkylating agents in the treatment of chronic myelogenous leukemia.

TABLE 21. Effect of Mitomycin C to Alkylating Agents Treated Cases of Chonic Myelogenous Leukemia

	I course	II	III	IV	V
1. F 61	BUSULFAN	NITROMIN	MMC	MMC	
2. F 43	THIO-TEPA	NITROMIN	MMC		
3. M 34	NITROMIN	TOYOMYCIN	6MP	MMC	MMC
4. M 42	AL-NM	BUSULFAN	THIO-TEPA	MMC	
5. F 44	TRENIMON	MMC	MMC		
6. M 38	BUSULFAN	BUSULFAN	THIO-TEPA	MMC	
7. M 26	RC-4	MMC			
8. F 36	THIO-TEPA	ENDOXAN	MMC	MMC	

6 → ←6 months DURATION OF REMISSION

COMPLETE REMISSION PARTIAL REMISSION MMC NO EFFECT

d) Recovery of sensitivity to mitomycin C

Case 4: A girl 19 years old. Her chief complaints were pitting edema and palpitation. She had been treated 2 times with 5 mg of mitomycin C resulting in 2 remissions of 11 months and 4 months, respectively. In the 3rd course, endoxan was not effective.

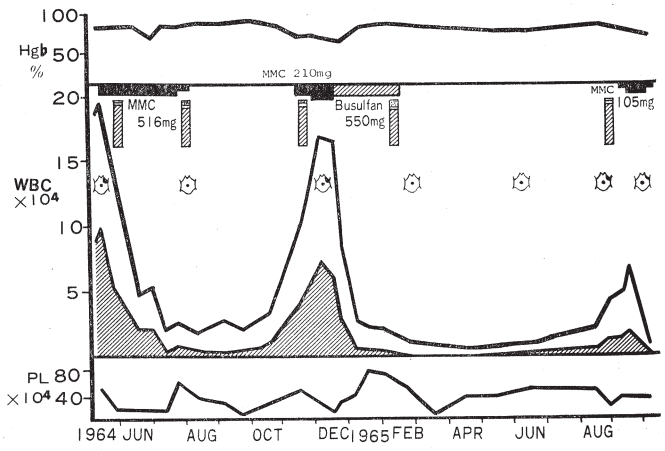


FIG. 13. Case 4.
Chronic myelogenous leukemia F. Age 19.

Fig. 14 shows the progress of this patient after the 4th course. After the 4th course, a remission for 3 months was obtained with 6 mg of oral

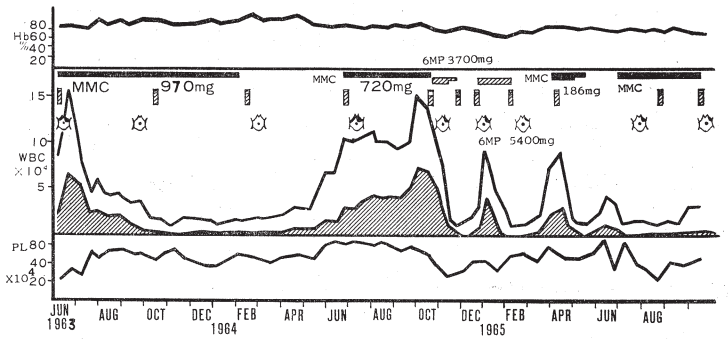


FIG. 14. Case 5.
Chronic myelogenous leukemia M. Age 46.

mitomycin C. After the 5th course, the patient became resistant to 6-9 mg of mitomycin C. An increase of the WBC, enlargement of the slpeen, and intensive anemia were observed in spite of the mitomycin C therapy. In the 6th course, 8 mg of busulfan was given to the patient. A remission was obtained and lasted for 7 months. On relapse from this remission with busulfan, 6-9 mg of oral mitomycin C was reintroduced as the 7th course. Two weeks later, the WBC decreased rapidly to 1,950 per cu. mm and splenomegaly diminished completely. With a total dose of 105 mg a remission for more than 6 months was obtained.

Case 5: (Fig. 12) A man 46 years old. His chief complaint was a dull pain in the left hypochondric region. He responded well to the first course of mitomycin C treatment and showed a remission for 9 months. However, the 2nd course of a total of 720 mg of mitomycin C (6 mg daily orally) for 120 consecutive days did not result in any improvement of his symptom. Next, a daily dose of 150 mg of 6 MP was given subsequently to the patient. By this 6 MP therapy, two remissions of 1 month and 2 months, respectively, were obtained.

For the 5th course, he again received treatment with 4-6 mg of mitomycin C. After 34 days and a total of 186 mg of mitomycin C, WBC dropped down to 8,400 per cu. mm and splenomegaly diminished.

The above two cases, who were resistant to mitomycin C, recovered the sensitivity to mitomycin C after treatment with busulfan or 6 MP. Furthermore, the improvement in symptoms was remarkably rapid at these times so that the sensitivity of the patients to mitomycin C was much greater than that occurring from the first course.

VI. DISCUSSION

Haut[11] described the duration of busulfan treatment necessary to normalize the leukocyte value as an exponential function of the white blood cell count at the time therapy was begun.

In the present study, the remission rate of patients with WBC of less than 10^5 was higher than those with WBC of 10^5 or more. The days and the dose required to achieve remission for the group with WBC of less than 10^5 were almost one half of that required for the group with WBC of 10^5 or more. These results indicate the presence of a close relation between WBC and the effect of mitomycin C. However, no statistical significance was observed in the duration of remission between the two groups.

A similar relationship was observed between two groups in which there was the presence and the absence of myeloblast in the peripheral blood. The remission rates were higher when the percent of immature leukocyte in the peripheral blood was less than 39%, the percent of myeloblast in bone marrow was less than 1%, and the hemoglobin percent was 80% or more. From the above results, it was assumed that the important factors regulating the response of patients to mitomycin C were WBC and myeloblast in the peripheral blood.

In terms of physical signs, the remission rate of patients with splenomegaly of less than 3 fb and patients without hepatomegaly was superior.

The remission rate by mitomycin C expressed in total cases was 77.3% and was considered to be equal to that of busulfan and of nitromin. However, the excellent remission cases with a score of 80 points or more were 56.9% of the total remission cases with mitomycin C and this rate was superior to the 27.3% with nitromin and 40.7% with busulfan.

The remission rate of intravenous mitomycin C therapy was much higher than of oral use.

Louis[54] reported that the incidence of acute blastic crisis was 59% in 27 cases of untreated patients. Haut[11] reported that 68% (15 cases out of 22) of acute crisis was found in patients treated with busulfan. Literature values report 58% of 153 cases with busulfan, 56% of 55 cases with X-ray + P^{32}. He concluded that approximately more than 50% of the patients, whether untreated or given busulfan, developed a blastic termination. However, Shimkin[56] reported an incidence of 25% in 64 untreated cases studied at autopsy. Wilkinson[57] came to the conclusion from his review that the incidence was increased in patients treated with chemotherapeutic agents. The present studies revealed an incidence of 61.6% of acute blastic crisis with mitomycin C and an incidence of more than 60% by other agents.

The life span of patients with this disease have been reported by several authors: 2.5 years in 52 cases with supportive therapy by Minot[53], 2.6 years

in 1,090 cases with X-ray or P^{32} by Tivey[59], 2.6 years in 118 cases with P^{32} by Reinhard[60]. Haut[11] reported 3.5 years in 30 cases with busulfan. In this paper the life span was 3.5 years with mitomycin C and 3.5 years with busulfan, which was similar to the results with busulfan by Haut.

Cases of drug resistance were reported by Haut[11] and by Till[9] with busulfan therapy. Hiramitsu[15] also reported a few cases who were resistant to busulfan, TEM, or thio-TEPA. In the treatment with mitomycin C, the development of resistance was rather infrequent and slow compared to other agents. Busulfan showed marked inhibitory effect in patients who were resistant to mitomycin C, and patients who were previously treated with various alkylating agents responded fairly well to mitomycin C.

These data might result in a conclusion that there was no cross resistance between mitomycin C and alkylating agents in the treatment of chronic myelogenous leukemia. The presence of cross resistance between mitomycin C and alkylating agents in rodent tumors have been reported by Kurita[43], Tsujiguchi[61][62], Oboshi[63], and Sugiura[64], and were incontrast to the results of chronic myelogenous leukemia. From this diversity, it might be assumed that resistance mechanisms might be different between rodent tumor and human leukemia. The difference in the resistance mechanisms could be explained partially by the great difference of drug dosage in the animal neoplasm system and in human leukemia. Furthermore, in human leukemia, host factors such as absorption, excretion, and detoxication of drugs influencing the blood levels of the drug are worth consideration.

It was suggested from the results that two patients resistant to mitomycin C recovered the sensitivity to mytomycin C. Saito[65] reported the recovery of sensitivity to 6 MP in a 6 MP resistant Yoshida ascites sarcoma after 10 generations of consecutive treatment with alanine nitrogen mustard. The present author[66] has observed that resistant cells completely disappeared from the mixed cell populations of the sensitive and the resistant L1210 mouse leukemia. The leukemia became sensitive to drugs when the mixed cell populations were transferred in mice for 5 to 19 generations without any drug therapy. This mechanism was mainly acconnted for by the difference in growth rate of the sensitive and the resistant leukemia cells.

The mechanism of recovery of sensitivity in the two patients is not clear at this moment. However, it might be speculated that this could be the result of the competition of resistant and sensitive leukemic cells and of some changes in host factors.

V. CONCLUSION

The effect of mitomycin C on chronic myelogenous leukemia was inves-

tigated from the view of the relation between the drug and the host factors, comparison with the effect of other agents, and drug resistance.

Patients with less hematological and clinical symptoms responded better to mitomycin C treatment; namely, those with less white blood cell count, less immature leukocyte and myeloblast in the peripheral blood, less anemia, less myeloblast in the bone marrow, less splenomegaly, less hepatomegaly, and less lymphadenopathy.

The therapeutic effect of mitomycin C is considered to be equal or be somewhat superior to the effect of busulfan as a result of data on the occurrence of resistance, cross resistance, development of acute blastic crisis, and life span.

Clinically, mitomycin C did not show cross resistance to alkylating agents. The recovery of sensitivity to mitomycin C in two patients might suggest a promising way of treatment in chronic myelogenous leukemia.

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