Carboquone Therapy for Hematologic Neoplasms

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UZUKA, Y., SAITO, Y., TAKAHASHI, H. and KOMATSU, M. *Carboquone Therapy for Hematologic Neoplasms*. Tohoku J. exp. Med., 1982, 138 (2), 151-160. — A daily oral dose of 1-2 mg of Carboquone was administered for remission induction to 38 patients with hematologic malignancy, and the following results were obtained: 2 of the 3 patients with malignant lymphoma, 1 of the 12 patients with multiple myeloma, 13 of the 14 patients with chronic myelogenous leukemia, and all 9 patients with polycythemia vera attained complete remission. — Carboquone; malignant lymphoma; multiple myeloma; chronic myelogenous leukemia

Carboquone (2,5-bis(1-aziridinyl)-3-(2-carbamoyloxy-methoxyethyl)-6-methylbenzoquinone) is an alkylating agent with quinone nucleus, ethyleneimino base and urethane base, all of which have been reported to manifest an anticancer activity and have a structure similar to those of mitomycin C and Trenimon.

Carboquone has been proved to have an excellent antitumor effect on transplantable experimental tumors and primary tumors. In humans, it has been used with some effect for treatment of myeloproliferative disorders, malignant lymphomas, lung cancer and others. The present study was undertaken to investigate the clinical effect of this agent on 38 patients with hematologic neoplasms admitted to our clinic.

MATERIALS AND METHODS

Patients. Thirty-eight patients with hematologic neoplasms including 3 patients with malignant lymphoma, 12 with multiple myeloma, 14 with chronic granulocytic leukemia, and 9 with polycythemia vera were subjected to this study.

Carboquone was administered by the oral route as a rule. Consecutive daily administration of 1 to 2 mg Carboquone was carried out for remission induction. For remission maintenance, 0.25 to 1.0 mg was administered every day, every other day or twice weekly depending upon the hematologic status.

Diagnostic criteria. Malignant lymphoma was diagnosed by histologic examination of the specimens obtained by operation or biopsy and classified for its stage according to ANN Arbor's criteria (Carbone et al. 1971). Multiple myeloma was diagnosed by the qualitative diagnosis of myeloma cells in reference to Costa's criteria (Costa et al. 1973). Chronic myeloid leukemia was diagnosed by hematologic findings, splenomegaly, a decreased alkaline phosphatase level of neutrophils, ph¹ chromosome and an elevated vitamine B₁₂

TABLE 1. *Criteria for evaluation of response to drug therapy in multiple myeloma*

Grade of Improvement								
	I	Score	II	Score	III	Score	IV	Score
Bone marrow plasmacytosis or plasma-cytoma	Significant decrease in marrow myeloma cells (less than 2%) or 50% or greater decrease in size of plasmacytoma	20	More than 50% decrease in marrow myeloma cells or 25-50% reduction in size of plasmacytoma	15	25-50% decrease in marrow myeloma cells	10	Unchanged or aggravated	0
Myeloma proteins	Recovery of serum protein to normal value	15	Decrease in serum protein by 2 g/100 ml or more	10	Decrease in serum protein by less than 2 g/100 ml	5	Unchanged or aggravated	0
	Significant (more than 50%) decrease in serum or urine myeloma proteins	10	25-50% decrease in serum or urine myeloma proteins	5	Less than 25% decrease in serum or urinary myeloma proteins	0	Unchanged or aggravated	0
Radiography of bones	Radiographic evidence of healing of bone lesions or skeletal recalcification	10	Improved	5	Unchanged or aggravated	0	Unchanged or aggravated	0
Hematologic findings	Significant rise in Hb (more than 12 g/100 ml) or RBC count (more than $350 \times 10^4/\mu\text{l}$)	15	Rise in Hb 2 g/100 ml or more or rise in RBC count ($300-350 \times 10^4/\mu\text{l}$)	10	Rise in Hb by less than 2 g/100 ml or rise in RBC count to less than $300 \times 10^4/\mu\text{l}$	5	Unchanged or aggravated	0
Erythrocyte sedimentation rate (ESR)	ERS less than 20 mm (1 hr)	10	ERS less than 50 mm (hr)	5	More than 50 mm (hr)	0	Unchanged or aggravated	0
Performance state	4→2, 1, 0 3→1, 0 2→0 1→0	10	4→3 3→2 2→1	5	Unchanged or advanced	0	Unchanged or aggravated	0
Subjective symptoms	Disappeared	10	Improved	5	Unchanged or aggravated	0	Unchanged or aggravated	0

Complete remission=80 score. Incomplete remission=50-79. Effective=30-49. Ineffective<30.

level, and polycythemia vera by the criteria of the National Polycythemia Vera Study Group (Joseph and Lous 1977).

Evaluation and criteria for remission. The efficacy of Carboquone was evaluated by Kimura's criteria in malignant lymphoma (Kimura 1969) by our original criteria in multiple myeloma (Table 1), by Kimura's criteria (Sakano and Kimura 1974) in chronic granulocytic leukemia, and by Gilbert's criteria (Gilbert 1968) in polycythemia vera.

RESULTS

Effect on malignant lymphoma. Three cases, each of Hodgkin's disease, lymphosarcoma and reticulosarcoma were treated with Carboquone. In the case of Hodgkin's disease, complete remission was obtained with a total dose of 81.5 mg and was maintained for 10 months. In the case of lymphosarcoma, Carboquone was used in combination with Bleomycin and FT-207. Complete remission was obtained and was maintained for more than 3 months. The dose of Carboquone administered was small and no effect was obtained in the case of reticulum cell sarcoma (Table 2).

Effect on multiple myeloma. Twelve patients with multiple myeloma were administered intravenously or orally with 0.5 to 1 mg Carboquone every day. The total dose of Carboquone ranged from 11.5 to 123.5 mg with a mean of 51.9 mg. The duration of treatment ranged from 14 to 192 days with a mean of 72.5 days. Despite relatively high doses and long-term administration of the drug, it was evaluated to be ineffective in all but 2 cases. Incomplete remission was attained in one and some effect in the other of these two cases (Table 3).

Effect on chronic myelogenous leukemia. Remission induction was carried out in 14 cases with Carboquone, of which 8 were previously untreated and the remaining 6 had previously been treated with Busulfan or Dibromomantol. The initial dose of Carboquone in remission induction varied from 1 to 2 mg per day, favoring an oral dose of 1 mg of the drug. Out of 14 cases, 13 attained complete remission. The time from the initiation of therapy to a decrease in white blood cell count to about 10,000 ranged from 14 to 104 days, with a mean of 40.7 days. The time until an enlarged spleen reduced to one-third or smaller ranged from 14 to 84 days with a mean of 35.9 days. When remission was achieved, the doubling time of the WBC was measured in 9 cases. It ranged from 14 to 118 days, being shorter than 4 weeks in 6 of them. Thus, we decided that maintenance treatment was necessary in many cases. Patients were placed on continuous Carboquone treatment with doses of the drug adjusted to maintain the WBC count between 8,000 and 15,000/mm³. Usually a daily dose of 0.25 to 0.75 mg of the drug was administered every other day or twice weekly. The median survival time from the initiation of Carboquone therapy was 40.5 months. The development of blastic crisis was observed in 57.1% of the patients treated with the drug (Table 4).

Effect on polycythemia vera. All 9 cases achieved complete remission by consecutive daily administration of 1 to 1.5 mg Carboquone. The time until complete remission ranged from 14 to 83 days with a mean of 48 days. For maintenance of remission, 0.25 to 0.75 mg of the drug was administered every day,

TABLE 2. *Response to Carboquone*

Case	Age	Sex	Diagnosis	Stage of disease	Previous treatment
1. A.A.	55	M	Hodgkin's disease	IVb	(—)
2. M.T.	48	M	Lympho-sarcoma	IIa	(—)
3. M.S.	42	M	Reticulo sarcoma	IVb	ET-207

TABLE 3. *Response to Carboquone*

Case	Age	Sex	Diagnosis	Previous treatment	Method of CQ administration (mg $\times$ days)
1. M.O.	52	M	Multiple myeloma (IgG)	PSL. Cyt	1 $\times$ 22 every day i.v.
2. T.K.	71	F	" (IgG)	(—)	1 $\times$ 25 every day i.v.
3. T.K.	69	F	" (IgG)	(—)	1 $\times$ 32 every day i.v.
4. H.K.	68	M	" (B-J)	(—)	3 $\times$ 4 twice weekly i.v.
5. T.Y.	62	M	" (IgG)	(—)	1 $\times$ 14 every day i.v.
6. S.S.	75	F	" (IgG)	Cyt	0.5 $\times$ 164 every day p.o.
7. S.S.	73	M	" (IgA)	(—)	0.75 $\times$ 128 "
8. T.N.	52	M	" (IgG)	Cyt	0.5 $\times$ 150 every day p.o.
9. K.S.	46	F	" (IgG)	(—)	1.5 $\times$ 30 every day p.o.
10. R.S.	54	M	" (IgG)	(—)	0.5 $\times$ 23 every day p.o.
11. H.K.	59	F	" (IgG)	PSL. Cyt.	1 $\times$ 29 every day p.o.
12. F.K.	59	F	" (IgA)	PSL. Cyt	0.5 $\times$ 80
					1 $\times$ 110 every day p.o.
					0.5 $\times$ 27
					1 $\times$ 21 every day p.o.
					0.5 $\times$ 97
					1 $\times$ 21 every day p.o.

or once or twice weekly. This maintenance treatment kept the RBC count and hematocrit value at a relatively stable level in most cases. Moreover, discontinuation of the drug after achieving remission was possible in 2 cases. As for side effects, leukopenia and thrombocytopenia were observed along with reduction of the RBC count. However, the decrease of the WBC count to less than 3,000/mm³ and that of the platelets to less than 100,000/mm³ were observed in only one case. Although the RBC count was decreased to less than 4,000,000/mm³ during treatment in 3 cases, it recovered to the normal level in a short time of 1 to 2 weeks after discontinuation of the drug (Table 5).

Side effects. Toxicity appeared to be restricted to the hemopoietic system.

of malignant lymphoma

Method of CQ administration	Total doses (mg)	Effect	Side effects	Survival time
1 mg/day $\times$ 19 i.v. every day	49	Incomplete remission	(—)	1 year and 9 months
2 mg/day $\times$ 15 i.v. twice weekly				
1 mg/day $\times$ 19 p.o. every day				
0.5 mg/day $\times$ 27 p.o. every day	32.5	Complete remission	(—)	
1.5 mg/day $\times$ 33 p.o. every day	49.5	Complete remission	(—)	3 months+
1 mg/day $\times$ 7 p.o. every day	7	Ineffective	Anorexia	10 months

of multiple myeloma

Total dose (mg)	Duration of administration (days)	Effect	Side effect	Survival time
22	22	Ineffective	Leukopenia	8 months
25	25	"	Leukothrombopenia	Unkown
44	46	"	"	2 years and 2 months+
14	14	"	Thrombopenia	1 months
103	192	"	(—)	3 years and 5 months
75	150	"	(—)	3 years and 4 months
45	45	"	Leukopenia	2 yeras
11.5	23	"	"	1 year
69	109	"	"	2 years and 5 months
123.5	137	Complete remission	Anorexia	2 years and 4 months+
69.5	118	Effective	(—)	6 years and 2 months
21	21	Ineffective	(—)	3 years and 8 months

The gastrointestinal side-effects were rather insignificant.

DISCUSSION

As for the effect of Carboquone on malignant lymphoma, complete remission was obtained in one case each of both Hodgkin's disease and lymphosarcoma. Since the number of cases is very small, a further study is necessary. However, the effectiveness of the drug on malignant lymphoma has been demonstrated by several investigation (Hasegawa et al. 1973; Shirakawa et al. 1976).

Carboquone induced complete remission in one and was evaluated to be effective in another one of the 12 patients with multiple myeloma. It was ineffective in all

TABLE 4. *Response to Carboquone*

Case	Age	Sex	Previous treatment	Induction therapy	Effect	Maintenance therapy		
				Method of CQ administration (p.o. mg/ every day × days)		Method of CQ administration (p.o. mg/ every day)	Duration (days)	Effect
1. K.K.	64	M	Myleran	1.5 × 24	C.R.	0.25-1.0	435	Effective
2. F.K.	65	F	(-)	1 × 45	C.R.	0.25-1.0	435	Effective
3. K.S.	37	F	(-)	1 × 34	C.R.	0.25-1.0	212	Effective
4. R.K.	54	M	DBM	1 × 14 + 1.5 × 14	C.R.	0.5 -1.0	329	Effective
5. I.S.	43	M	Myleran	1 × 14	C.R.	0.5 -0.75	317	Effective
6. N.O.	28	M	DBM	1 × 28	C.R.	0.5 -1.0	532	Effective
7. K.T.	57	M	(-)	1 × 49	C.R.	0.5 -1.0	266	Effective
8. Y.S.	34	F	(-)	1.5 × 122	C.R.	0.5	567	Effective
9. M.M.	70	F	(-)	1 × 34	C.R.	0.25-0.75	620	Effective
10. T.S.	62	M	(-)	1 × 28	C.R.	0.5 -1.0	749	Effective
11. H.K.	16	F	(-)	1.5 × 56 + 1 × 14	C.R.	0.5 -0.75	318	Effective
12. T.S.	24	F	DBM	1 × 14 + 1.5 × 34	C.R.	0.75-1.0	140	Effective
13. A.T.	46	M	DBM	1 × 28	C.R.	0.75	118	Effective
14. K.K.	66	M	(-)	2 × 91	InC.R.	/	/	/

C.R., complete remission; InC.R., incomplete remission. * (): WBC doubling time.

of the remaining cases. Carboquone therapy of multiple myeloma attempted so far offered only little benefit to the patients. Our results provided a confirmation of several other investigations (Farhangi and Ossermam 1973; Bersagel 1976).

As for the effect of Carboquone on chronic granulocytic leukemia, 13 out of 14 patients (93%) achieved complete remission by consecutive daily oral administration of 1 to 2 mg of the drug. The mean and median periods until complete remission were 35.8 and 35 days, respectively. The results are comparable to those obtained with Dibromomanitol and more excellent than those obtained with Busulfan.

of chronic myeloid leukemia

Optimal maintenance dose (mg/day)	Total dose (mg)	Time until reduction of splenomegaly to 1/3 or smaller (days)	Time until terminal phase	Survival time after diagnosis	Subsequent treatment
0.25-0.5	36	40	8 months (8 months) [†]	11 months	(-)
0.25-0.5	251.25	/	2 years (1 year and 11 months)	2 years	(-)
0.25-0.5 (26 days)*	156.25	21	3 years and 3 months (1 year and 11 months)	3 years and 4 months	(-)
0.5 -0.75 (28 days)	227	14	2 years and 10 months (1 year and 4 months)	3 years	(-)
0.5 -0.75	174.5	14	4 years and 4 months (11 months)	4 years and 6 months	(-)
0.6 -0.75 (14-28 days)	459.5	84	2 years and 3 months (1 year and 9 months)	2 years and 4 months+	(-)
0.5- 0.75 (28 days)	157.5	/	/	11 months+	(-)
0.5	653	/	/	2 years and 1 month+	(-)
0.25 3/week to every day (26 days)	334	37	/	1 year and 11 months+	(-)
0.5 -0.75 (42 days)	519.25	28	/	2 years and 4 months	(-)
0.5 -0.75 (14-28 days)	213	57	/	2 years and 4 months+	(-)
0.75-1.0	132.75	/	/	1 year and 7 months+	(-)
0.75-1.0 (118 days)	116.5	28	/	5 years and 8 months+	Splenectomy Myleran
/	182	/	/	4 months+	Myleran

[†] (): Time until terminal phase after initiation of CQ administration.

As for the the effect of the drug on the decrease of splenomegaly, there exists some controversy (Hasegawa et al. 1973). However, a rapid reduction of splenomegaly parallel with a decrease of the WBC count was observed in the present cases. The effect was comparable to those of Dibromomanitol and superior to Busulfan. With regard to the maintenance of remission, continuous maintenance treatment was needed in most patients. An optimal maintenance dose was decided in relation to the doubling time of the WBC count. The dose with which the doubling time of WBC count was obtained in about 4 weeks was first determined. A dose slightly

TABLE 5. *Response to Carboquone*

Case	Age	Sex	Previous treatment	Dose of CQ and	
				Remission induction	
				Method of administration	Effect
1. A.K.	41	M	Cyt. Myleran, Melpharan, Venesection	1×26	C.R.
2. H.N.	55	F	MMC, Myleran	1×14	C.R.
3. J.W.	63	M	Myleran	1×39	C.R.
4. M.M.	50	F	³² P, Venesection	1×69	C.R.
5. H.Y.	58	F	Myleran, Vercyte	1×49	C.R.
6. H.S.	58	F	(-)	1×43	C.R.
7. T.O.	59	M	(-)	1.5×48	C.R.
8. T.T.	60	M	VDS	1.5×56	C.R.
9. T.K.	73	F	(-)	1×83	C.R.

C.R., complete remission.

larger than it could be used as an optimal maintenance dose to keep the WBC count at a constant level of approximately 10,000/mm³. The dose was determined to be a consecutive daily administration of 0.25 to 0.75 mg.

Several reports indicated that leukemic cells become resistant to this drug more rapidly than to others (Hasegawa et al. 1973). In our study, however, it was difficult to confirm this. The incidence of blastic crisis in patients treated with Carboquone until March 1979 was 57.1%, which was lower than the 75% and 72.7% obtained with Busulfan and Dibromomanitol, respectively. As mentioned above, Carboquone is comparable to Busulfan and Dibromomanitol in efficacy. In addition, this drug is free of such severe side effects as the pigmentation, amenorrhea, and lethal pulmonary fibrosis reported for Busulfan and Dibromomanitol (Spiers 1976). Thus, Carboquone is considered to be a very useful drug for treatment of chronic myeloid leukemia. We induced remission with relatively

of polycythemia vera

clinical effect		Side effects	Survival time after diagnosis	Subsequent treatment
Maintenance				
Method of administration	Effect			
Intermittently 0.5 mg twice weekly	Effective	(—)	6 years and 4 months+ (2 years and 3 months)	(—)
Intermittently 1 mg twice weekly	Effective	(—)	11 years and 2 months+ (2 years and 3 months+)	(—)
Intermittently 0.5 mg once weekly	Effective	(—)	5 years and 8 months+ (2 years+)	(—)
Intermittently 0.5–0.75 mg/ every day	Effective	(—)	2 years and 2 months+ (1 year and 9 months+)	(—)
Intermittently 0.5 mg/every day	Effective	(—)	14 years+ (1 year and 9 months+)	(—)
Intermittently 0.5 mg/day once or twice weekly	Effective	Thrombo- cytopenia	7 months+	(—)
0.75 mg/day twice weekly or every day	Effective	(—) Leukopenia	1 year and 5 months+ (1 year and 5 months+)	(—)
0.25–0.5 mg/every day	Effective	(—)	1 year and 7 months+ (1 year and 5 months+)	(—)
0.25–0.75 mg/day weekly or 5 per every day	Effective	(—)	8 months+ (8 months+)	(—)
(—): Time until terminal phase after initiation of CQ administration.				

(): Time until terminal phase after initiation of CQ administration.

small doses of Carboquone. Recently, it has been reported that aggressive treatment is effective for chronic phases of the disorder (Goldman 1978; Douglas and Wiltshaw 1978). Carboquone should be examined from this point of view.

The report of Hasegawa et al. (1973) was probably the first one to draw attention to the effectiveness of Carboquone on polycythemia vera. This was confirmed by the present study. The drug has advantages over venesection, ³²P treatment, or various alkylating agents such as Vercyte, Melphalan, Chrorambucil, Dibromomanitol and Busulfan, indicating more reliable effectiveness, less frequent side effects, and the feasibility of obtaining long lasting remission with or without continuous maintenance therapy. Thus, Carboquone has proved to be a most promising drug for the treatment of polycythemia vera. Some authors reported that resistance to this drug appeared easily in polycythemia vera as in chronic myeloid leukemia. In the present cases, however, the maintenance dose

had to be increased within a year in only one case.

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