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Short communication

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Treatment of acute myeloid leukemia and blastic phase of chronic myeloid leukemia with combined eflornithine (alpha difluoromethylornithine) and methylglyoxal-bis-guanyl hydrazone (methyl-GAG)

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Summary. A combined eflornithine-MGBG treatment was studied in patients with acute myeloid leukemia (AML) or blastic transformation of chronic myeloid leukemia (BT CML). The first ten patients (5 AML, 5 BT CML) received i.v. or p.o. eflornithine 6 g m^{-2} day-1 and i.v. MGBG 500 mg/m^2 once a week. The duration of treatment was 5–37 days (median 15) with one to five MGBG infusions (median 2). The results were complete response (CR) in one patient, partial response (PR) in four, minimal response (MR) in one and failure (F) in four. Pronounced side effects, including severe mucositis, gastrointestinal disturbances and skin infiltration, were observed in eight patients. As the four PRs were achieved in patients with BT CML, it was decided also to study ten patients with this indication. In attempts to decrease the incidence and severity of unwanted effects, lower doses of eflornithine-MGBG were used, i.e., eflornithine 4 g m^{-2} day-1 and MGBG 200 mg m^{-2} once a week. The duration of treatment was 9–110 days (median 46), with 2–14 MGBG infusions (median 6). Responses observed were CR in two patients (in one of whom it was only transient), transient PR in two, transient MR in four, and F in two. Treatment at lower doses was better tolerated, thus allowing a longer duration of treatment. Five of ten patients had moderate or severe gastrointestinal disturbances and one patient had a severe subjective hearing loss. The eflornithine-MGBG combination may prove to be a useful alternative treatment for AML and BT CML, but comparative trials will ultimately be necessary for a more definitive assessment of the combination.

Introduction

Methylglyoxal-bis[guanyl-hydrazone] (MGBG, mitoguazone, methyl-GAG) is a cytotoxic compound whose activity in the treatment of acute leukemia was first demonstrated more than 20 years ago [3, 4, 6, 15, 16, 18]. However, because of significant toxicity, MGBG was largely abandoned. The renewed interest for this drug is mainly due to the description of less toxic dosage schedules whether MGBG is administered alone or in combination with other anticancer agents [24]. Although the precise antitumor mechanism of MGBG is not known, it seems it may be related to an inhibition of polyamine biosynthesis [10].

Eflornithine (alpha difluoromethylornithine, DFMO) is an irreversible inhibitor of ornithine decarboxylase (ODC), a key enzyme in the biosynthesis of polyamines, so that its administration leads to a depletion of intracellular polyamines [17]. It has been reported that such an effect will enhance the cellular uptake of exogenous polyamines and of their structural analogues such as MGBG, a phenomenon that can therefore be used to augment the antiproliferative activity of MGBG [1, 19, 21].

This observation provided the rationale for the study of an eflornithine-MGBG combination in humans. In the first clinical trial an impressive clinical response was observed, with mild toxicity or none at all [20]. We therefore decided to study this combination in adult patients with acute myeloid leukemia (AML) or with blastic transformation of chronic myeloid leukemia (BT CML). We studied two groups of ten patients.

Patients and methods

Patients with AML resistant to previous conventional therapies and patients with cytogenetically confirmed BT CML, whether previously treated or not, were eligible for the study. All selected patients were adult and had given informed consent to inclusion in the study.

Pretreatment evaluations included: history of clinical symptoms, physical examination, hemogram, bone marrow examination (by aspiration and biopsy) for morphologic and cytogenetic studies, coagulation tests, liver and renal functions and chest X-rays. The clinical examination and the blood biochemical and hematological tests were repeated once weekly during the treatment and at the end.

The criteria of response to treatment were based upon changes observed in the counts of leukemic cells. In AML, a complete response (CR) corresponded to complete disappearance of leukemic cells in bone marrow or to a residual rate of $<5\%$; a partial response (PR), to a decrease in leukemic cells by $>50\%$ in bone marrow and/or in blood; a minimal response (MR), to a decrease by $<50\%$ in bone marrow and/or in blood; and a failure (F) of treatment, to worsening or unchanged results. In BT CML, a CR was defined as a return to the chronic phase of the disease (i.e., disappearance of leukoblasts or decrease in myeloblasts + promyelocytes to $<30\%$ in bone marrow and/or in blood); PR, MR, and F were defined as for AML.

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Table 1. Patient characteristics, treatments and therapeutic responses in part one of study

Patient no. sex/age (years)	Diagnosis[a]	Treatments				Results		
		Eflornithine		MGBG		Blast cells[b] at start → end of study		Response[c] (end of study)
		Dose (gm^{-2} day^{-1})	No. of days	Dose (mg/m^2 i.v.)	No. of doses	Blood ($\times 10^3/mm^3$)	Bone marrow (%)	
1. F/53	AML (M_1)	6.0 i.v.	5	500	1	0 → 0	78 → blastic aplasia	F
2. F/57	AML (M_4)	6.2 p.o.	13	517 620	1 1	0 → 0	36 → 0	CR
3. F/52	AML (M_5)	5.6 p.o.	13	500	2	0.016 → 0.6	58 → blastic aplasia	F
4. F/66	AML (aplastic form)	5.7 p.o.	10	506	1	0 → 0	58 → 74	F
5. F/55	AML (secondary)	5.8 p.o.	16	451 355	1 1	83 → 7.2	61 → 59	F
6. M/25	BT_1CML	6.0 p.o.	31	500 600	1 1	0 → 0	HB: 43 → 12	PR
7. F/66	BT_1CML	5.6 p.o. 5.6 i.v.	4 10	500	2	74 → 0.25	HB: 81 → n.a.	PR
8. M/57	BT_1CML	5.9 p.o. 5.9 i.v.	32 5	500	5	72 → 0	HB: + → n.a.	PR
9. M/48	BT_2CML	6.3 p.o. 4.2 i.v.	15 14	500	4	13.4 → n.a.	MB + PM: 45 → 29	MR
10. F/25	BT_1CML	6.2 i.v. 2.9 i.v. 2.2 i.v.	3 3	222	3	19.4 → 3.0	HB: 90 → n.a.	PR

[a] AML recorded according to FAB classification (Br J Haematol 33: 451, 1976). However, patients 4 and 5 could not be classified because of atypical morphologic presentations. BT_nCML, blastic transformation of CML; n indicates the number of blastic episodes at entry on study

[b] HB, hemoblasts; MB + PM, myeloblasts + promyelocytes; +, presence; n.a. not available

[c] CR, complete response; PR, partial response; MR, minimal response; F, failure of treatment (see "Patients and methods" for the criteria of response)

Results

Part one of study[1]

The ten patients were seven women and three men, with a mean age of 50.4 years (range 22–66). Five had AML, and five were suffering from their first or second (Pt 9) episode of BT CML (Table 1). All were resistant to the conventional therapies previously given (mean number of cytotoxic drugs: 1.7; range: 1–3).

Eflornithine was administered p.o. or i.v. (Table 1) at the starting dose of 6 g/m^2 body surface area daily in three divided doses. MGBG was started 3–4 days later and given as a slow (3 h) i.v. infusion of 500 mg/m^2 once a week. Doses were subsequently adjusted according to individual tolerance and hematological responses (Table 1). The duration of the treatment varied from 5 to 37 days (median 15 days) and the number of MGBG infusions, from 1 to 5 (median two infusions).

All patients experienced bone marrow aplasia. One CR was observed (Pt 2). PR was observed in four patients (Pts 6, 7, 8 and 10), all of whom were being treated for BT CML. An MR was noted in one patient (Pt 9), and four patients (all with AML) failed to respond to treatment (Pts 1, 3, 4 and 5).

Pronounced side effects were observed in eight of the ten patients; the most frequent were mucositis ($n = 7$), gastrointestinal complaints ($n = 7$) and skin infiltration ($n = 5$).

As these results were suggestive of therapeutic activity in BT CML, it was decided to extend the study in ten patients with this indication. In an attempt to decrease the incidence and severity of unwanted side effects, lower doses of eflornithine-MGBG were administered.

Part two of study

Ten patients (7 male, 3 female) aged 20–66 years (mean 41.7 years) were included (Table 2). Seven were in the first (Pts 2–6, 8 and 9), 2 in the second (Pts 7 and 10), and one in the third (Pt 1) episode of BT CML. With the exception of patient 6, in whom CML had not been recognized before the diagnosis of BT CML, all patients had been treated with chemotherapeutic agents (mean 4.7; range 2–11). Two patients (Pts 7 and 10) had previously recovered from ALL before developing CML. Other previous treatments included splenectomy (Pts 5, 9 and 10) and radiotherapy to the spleen (Pts 1, 7 and 10). Patient 1 had already received the eflornithine-MGBG combination 6 months before, having been included in part one of this study during his second episode of BT CML.

Eflornithine was administered p.o. or i.v. (Table 2) at the starting dose of 4 g/m^2 daily given in three divided

[1] Results presented in part at the Second European Conference of Clinical Oncology [7]

Table 2. Patient characteristics, treatments and therapeutic responses in part two of study

Patient no. sex/age	Diagnosis[a]	Treatments				Results			
		Eflornithine		MGBG		Blast cells[b]			Response[c]
		Dose (gm^{-2} day^{-1})	No. of days	Dose (mg/m^2 i.v.)	No. of doses	Day of study	Blood ($\times 10^3/mm^3$)	Bone marrow (%)	
1. M/49	BT_3CML	4.3 p.o.	2	162	3	0	0.12	HB: 50	–
		4.3 i.v.	26	216	1	19	7.8	38	MR
						26	7.8	67	F
2. M/46	BT_1CML	4.2 i.v.	48	211	3	0	49.3	MB + PM: 23	–
				301	3	6	9.75	n.a.	PR
						47	41	23	F
3. F/66	BT_1CML	4.2 i.v.	12	209	2	0	23.7	MB + PM: 28	–
						12	61.6	n.a.	F
4. M/41	BT_1CML	4.1 i.v.	9	276	5	0	140	HB: not interpretable	–
						9	432	46	F
5. F/20	BT_1CML	4.1 p.o.	26	176	5	0	18.5	HB: 33	–
				294	2	5	0.32	n.a.	PR
						26	1.69	n.a.	MR
6. M/45	BT_1CML	3.9 p.o.	79	202	4	0	32.8	HB: 20	–
				123	2	36	1.08	17	MR
				202	1				
				307	2	78	0.62	48	F
7. M/51	BT_2CML	4.0 p.o.	110	200	1	0	10.1	MB + PM: 36	–
				273	1	32	0.53	29	PR
				333	1	60	0.35	18	CR
				303	9				
				212	2	110	0	9	CR
8. F/26	BT_1CML	3.9 p.o.	29	215	2	0	55.4	MB + PM: 42	–
		0	9	368	1				
		3.9 p.o.	44	307	1	25	2.7	9	CR
				92	1				
				307	1				
				215	1				
				307	1				
				368	1	84	11.8	29	F
9. M/35	BT_1CML	3.8 p.o.	64	208	1	0	64.9	HB: 46	–
				298	3	14	20.7	36	MR
				208	1				
				298	4	64	2.5	51	F
10. M/38	BT_2CML	3.2 p.o.	46	189	1	0	1.6	MB + PM: 32	–
				270	4	31	15.5	28	MR
				324	1	38	5.88	28	F
						46	3.26	n.a.	

[a] BT_nCML, blastic transformation of CML; n indicates the number of blastic episodes at entry into study
[b] HB, hemoblasts; MB + PM, myeloblasts + promyelocytes; +, presence; n.a. not available
[c] CR, complete response; PR, partial response; MR, minimal response; F, failure of treatment (see "Patients and methods" for the criteria of response)

doses. Usually 3–5 days (except Pt 6, 7 days) later, MGBG was started at a dose of 200 mg/m^2 once a week, given as a slow (3 h) i.v. infusion. Individual treatment schedules are summarized in Table 2. The duration of treatment varied from 9 to 110 days (median 46 days) and the number of MGBG infusions, from 2 to 14 (median 6 infusions).

The therapeutic results are shown in Table 2, which shows both the best response recorded during the treatment and the final response when the treatment was terminated. Two patients (Pts 3 and 4) did not respond to treatment. Four patients (Pts 2, 5, 7 and 8) responded favorably: two patients (Pts 2 and 5) achieved PR that was later followed by failure (Pt 2) or MR (Pt 5); patients 7 and 8 returned to the chronic phase (according to cytological criteria), but patient 8 subsequently relapsed and did not respond to further eflornithine-MGBG treatment. The other four patients (Pts 1, 6, 9 and 10) had minimal and transient responses.

The treatment was perfectly well tolerated in five of the ten patients (Pts 1, 3, 4, 5 and 7). In the other five patients the major side effects were related to mild to moderate (Pts 2, 8, 9, 10) or severe (Pt 6) gastrointestinal disturbances, and one patient (Pt 2) developed a severe subjective hearing loss.

Discussion

Despite the large number of antineoplastic agents used and the variety of therapeutic schedules tested, the treatment of relapsed AML remains a difficult problem [13]. The same is also true for the blastic crisis of chronic myeloid leukemia [27], which leads to early death in all patients. In attempts to control this blastic phase better, recent trials have used intensive polychemotherapy [2, 5, 22] and bone marrow transplantation [8].

The obvious need for more effective treatments has led investigators to look for specific potentiation of drug already known to have therapeutic activity in hematological diseases. MGBG as a single agent is known to have antileukemic properties [16], and combinations of MGBG with other drugs have shown activity in acute leukemia [3, 4, 9, 14, 18], in lymphoma [11, 12, 25] and in some solid tumors [24]. The observation that eflornithine-induced depletion of intracellular polyamine concentrations could enhance the intracellular uptake of MGBG preferentially into tumor cells [19] stimulated interest in the chemotherapeutic potential of this particular combination.

The results observed with our first ten patients were promising, with one CR observed in five AML cases and four PRs in five BT CML patients. The combined treatment was poorly tolerated, however, as has been described in recent phase I trials [23, 26]. We therefore, decided to study ten cases of BT CML in addition, using lower doses of each drug in an attempt to improve tolerance. The lower doses were in fact, generally better tolerated. The best evidence of improved tolerance is probably the observation that the total duration of treatment, and therefore the number of MGBG infusions, was three times greater in the second part of the study. The therapeutic responses observed with these lower dosages were quite variable. Although eight of the ten patients showed some degree of improvement during the study, only one response was sustained.

The results of the present study, then, indicate that the eflornithine-MGBG combination may prove to be a useful alternative treatment for AML and BT CML. At the doses administered in the second part of the study, i.e., eflornithine 4 g/m^2 per day (i.v. or p.o.) and MG BG 200 mg/m^2 per week (i.v.), the treatment was reasonably well tolerated and yielded various degrees of therapeutic responses in BT CML. However, because the present study was not designed as a comparative trial between two different dosages of the drug combination, no definitive conclusion can be drawn as to whether these represent the optimal doses of eflornithine-MGBG for use in all patients. Specifically designed comparative trials will ultimately be necessary for a more definitive assessment of the combination.

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