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[131I]-Metaiodobenzylguanidine in the treatment of metastatic neuroblastoma*

Clinical, pharmacological and dosimetric aspects

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Summary. Ten children with stage III or IV neuroblastoma that had either relapsed or was refractory were treated with [^{131}I]-metaiodobenzylguanidine (MIBG) from 1984 to 1986. The total dose ranged from 4,365 to 21,900 MBq and was given in one to five courses. Two patients achieved a complete remission (CR), two, a partial remission (PR), and three, an arrest of the disease. Pharmacological studies showed that 93% of detectable radioactivity was attributable to MIBG at the beginning of the infusion. However, by the end of the infusion this had decreased to 88%. The terminal half-life of MIBG was 37.0 h, whereas that of non-MIBG-bound iodine was 71.6 h. Therefore, the radioactivity-time product of non-MIBG-bound ^{131}I was much higher than that of MIBG. Dosimetric studies showed a mean level of absorbed radiation for the total body of 160 μGy/MBq, a liver irradiation of 540 μGy/MBq and a mean tumour radiation of 10,500 μGy/MBq.

Introduction

Structural analogues of norepinephrine have been used for several years in clinical medicine. Benzylguanidine is a compound closely related to guanethidine that is selectively taken up and stored by sympathetic nerve tissue [12]. Labelled with ^{123}I or ^{131}I, it can be used for scintigraphic imaging of adrenal medulla [21], pheochromocytoma [15] and neuroblastoma [9, 16]. The latter tumour still poses one of the biggest problems in paediatric oncology. Despite promising early results, neither autologous nor allogeneic bone marrow transplantation (BMT) have fulfilled expectations [2]. Conventional and highly intensive therapeutic regimens, including chemotherapy, surgery and external radiation, have resulted in survival rates of only 5%–10% [1].

After demonstrating that an active transport system in several cell lines takes up MIBG and, hence, a greater percentage of storage cells are killed than non-storage cells [3], we decided to use this substance for the first time in treating children who had not responded to chemotherapy [10]. This substance had previously been used only in trials involving pheochromocytoma [11]. Some of our preliminary findings in this area have been partially reported elsewhere [17, 18]. However, the present report summarizes all of our therapeutical experience to date in this area. Furthermore, our investigations of the pharmacokinetic properties of MIBG and its radiological side effects, as well as the total body and tumour doses attainable, are also described.

Patients and methods

Patient characteristics. We treated ten children (five boys and five girls) between the ages of 1 and 9 years (Table 1). At the time of initial diagnosis, two had stage III and eight had stage IV disease (staged according to Evans et al. [5]). Our patients were chosen at random from children who either had been referred to our centre for treatment of neuroblastoma or had previously undergone such treatment at our centre. Six of the children were still undergoing cytostatic therapy and began treatment with MIBG when the tumour showed signs of progression. Four children were treated during relapse of a stage III ($n = 1$) or stage IV neuroblastoma ($n = 3$). The duration of remission in these four cases ranged from 17 to 38 months. All patients had been treated according to established protocols from the German Society of Paediatric Oncology neuroblastoma studies NBL 79, NBL 82 or NB 85[1] (or similar protocols in the case of patients who had been treated outside the FRG). In addition to aggressive chemotherapy (Table 1), these protocols specified guidelines for surgical excision of primary tumours and radiation of remaining solid tumours.

Before MIBG therapy, the extent of tumour mass was measured in the abdomen by ultrasonography, in the chest and bones by X-ray, and in both the chest and abdomen by computerized axial tomography (Table 3). Scintigraphic imaging, clinical examination and laboratory parameters including catecholamines in serum, urine and blood and liver, kidney, thyroid and adrenal function were also used for evaluation. Bone marrow involvement was assessed by means of bone biopsy histology, marrow smears and, in some cases, autoradiography [6]. The ability of tumour sites to store MIBG was examined by MIBG imaging.

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[1] Study protocols of the GPO (Deutsche Gesellschaft für Pädiatrische Onkologie): NBL 79, 1979/1982; NBL 82, 1982/1985; NB 85, since 1985

Table 1. Patient characteristics before MIBG therapy

Patients	Age[a]	Sex	Stage[a]	Status[b]	Remission	Pretreatment
C.E.	2	M	IV	Refractory	–	3 × ACVCplVm
T.T.	2	M	IV	Refractory	–	4 × ACVD, 4 × CplVm, 2 × IVp
H.S.	5	F	IV	Relapse	38 months	3 × ACVD, 5 × AC
I.H.	3	F	IV	Relapse	23 months	5 × ACVD, 5 × CplVm
J.C.	2	F	IV	Refractory	–	5 × ACVD, 5 × CplVm
C.A.	3	F	III	Relapse	24 months	5 × ACVD, 5 × CplVm
J.E.	3	M	IV	Refractory	–	3 × ACVD, 3 × CplVm
M.G.	9	M	IV	Relapse	17 months	NA
N.M.	4	F	III	Refractory	–	2 × ACVD, 1 × CplVm
U.A.	1	M	IV	Refractory	–	IVp, ACVD, CplVm, 2 × ICpl

[a] At diagnosis
[b] At the beginning of MIBG therapy
A, Adriamycin; C, cyclophosphamide; Cpl, cisplatin; D, Dacarbacine; I, ifosfamide; V, vincristine; Vm, teniposide (VM 26); Vp, etoposide (VP 16); NA, data not available (treatment protocol in accordance with the South West Oncology Group)

Pharmacological studies. Venous blood samples were obtained immediately prior to treatment and then at 1, 2, 4, 8, and 24 h following infusion, as well as on each subsequent day for 7 days. Urine was obtained from spontaneously voided samples, which were kept at room temperature until analyzed. MIBG for clinical use was kindly supplied by Henning, Berlin, or purchased from Amersham Buchler (Braunschweig, FRG); it was shipped frozen and diluted with normal saline before administration. The measurement of MIBG was done by the HPLC method, as described elsewhere [4]. The chromatographic system consisted of a Waters M-45 solvent delivery system and a Waters model U6K injector. Separation was obtained with a Waters Associates Bondpak C_{18}-column (30 cm × 3.9 mm inside diameter, 10-μm particle size).

Nuclear medical investigations. The dose of incorporated activity was calculated using the MIRD computer programme (Medical Internal Radiation Dose), which is classified as so-called public domain software and was obtained from the College of Medicine, University of Florida (USA). In this programme the tabulated S-values (i.e. the fractions absorbed at the organ level), the body and organ sizes of a "reference man," certain organ activity parameters and geometrical relations are used to compute the total dose. However, in its original form this established procedural approach did not prove to be applicable in young patients. The need to take pediatric organ and geometrical relations into account initially precluded its use in the present study. However, the MIRD programme can now be applied to young patients as well, thanks to Henrichs' successful extension of the Monte Carlo computational procedure to determine S-values for the young at varying ages [8], where the modular character of the programme can be used.

During the input, a preprogramme is activated that effectively replaces the S-values and body dimensions of the "reference man" with corrected S-values and organ sizes for the young. The minimally altered MIRD-programme can then compute the required organ doses. Body and organ activity parameters required by the programme are monitored by a dual-probe whole-body scanner. An appropriate computer programme automatically corrects for any detected absorption loss, and a Gamma-11 system further evaluates these data. By fixing regions of interest, the Gamma-11 system can determine organ activity relative to a simultaneously scanned standard. The time-dependent activity concentrations in the individual organs thus monitored are fed into the MIRD programme, which can then provide a special print-out specifically for young patients.

Table 2. Cycles and doses of MIBG

Patients	Cycles	Total activity (MBq)	Total activity/ body weight (MBq/kg)	Activity/cycle × body weight (MBq/kg)	Schedule
C.E.	3	8,250	514	171	0.5-h infusion, day 1
T.T.	2	4,810	400	200	0.5-h infusion, day 1
H.S.	4	11,840	525	131	24-h infusion, day 1
I.H.[a]	5	21,900	1,457	291	24-h infusion, day 1
J.C.	3	9,060	695	231	24-h infusion, day 1
C.A.	2	5,550	277	139	24-h infusion, day 1
J.E[b].	2	12,910	1,402	701	4-h infusion, days 1 + 2
M.G.[b].	2	17,980	666	333	4-h infusion, days 1 + 2
N.M.[a].	1	4,365	318	318	4-h infusion, days 1 + 2
U.A.	1	8,810	370	370	4-h infusion, days 1 + 2
[A.K.[a]	1	6,216	414	414	24-h infusion, day 1]

[a] Patients in whom pharmacokinetic parameters were evaluated during one course of therapy
[b] Patients in whom pharmacokinetic parameters were evaluated during two courses of therapy

The final results of the particular organ-activity developments being investigated are presented in graph form, with tabular expression of the organ doses sought.

MIBG administration. In our nuclear medicine ward, infusions of MIBG were given over 0.5, 4 or 24 h (Table 2). These different schedules resulted from compromises between pharmacological and practical considerations. The first two patients received 0.5-h short-term infusions. At that time, we rejected administration by push-injection because of potential negative side effects such as hypertension or severe haemodynamic changes. The next four patients were given 24-h infusions, as in vitro data from our laboratory had shown that drug uptake was dependent on the duration of exposure [2]. From a more practical point of view (radiation exposure of nurses and parents, stability of the intravenous line during the night), a repeated 4-h infusion with a 24-h interval was chosen. Pharmacokinetic studies were done with both the 24-h and the 2×4-h regimen. In Table 2, patients who were evaluated pharmacokinetically are identified in the footnotes.

Doses changed during the investigation. The overall trend was to increase the dose after more data and experience with the substance was gained. Therefore, patients treated earlier were given doses between 131 and 200 MBq/kg. We later gave 701 MBq/kg to a body who was scheduled to receive an autograft directly after his MIBG course.

The thyroid was blocked with 500 mg/m^2 potassium iodide from day -3 onwards. Children remained on the ward until their body radiation dropped to the permitted level. Details concerning this treatment are covered elsewhere [17]. After completion of MIBG therapy, autologous bone marrow transplantation (BMT) was carried out in two children; another child received allogeneic bone marrow [2]. The treatment concept was approved by our clinic's ethics committee and informed consent was given by the parents.

Results

Clinical results

Two patients achieved a complete remission (CR)[2] (Table 3); both had stage IV disease at the time of MIBG treatment and both underwent autologous BMT after MIBG-induced remission. The first of these two patients, a girl, died after relapse of neuroblastoma in bone marrow about 170 days after transplantation. The other, a boy, recovered after MIBG treatment of a large abdominal tumour but died of bone marrow aplasia at the end of the pretreatment for transplantation (Fig. 1).

Two children achieved a partial remission (PR: 50%–90% reduction in measurable tumour, 0–1 bone marrow samples with tumour, all preexisting lesions improved on scan; HVA, VMA decreased by >90%) that lasted 8.5 and 4.5 months, respectively, but was followed by renewed tumour progression. In three children the disease was arrested and for several months (1.5, 1.5 and 12 months) no further progression was observed. Two of these children were the first ones treated with MIBG and had been given relatively low doses. Both children later died of tumour progression. In the third patient the tumour remained reduced for 12 months, after which the patient was lost to follow-up.

Three children did not respond at all to MIBG treatment. The first was a girl with stage III disease in relapse. There was no evidence of MIBG uptake, although uptake did take place during diagnostic imaging. The second was a boy with stage IV disease, who finally achieved a remission after undergoing repeat chemotherapy after MIBG treatment. In his case, transplantation was carried out using marrow from his identical sibling, but he later died of graft-versus-host disease (GVHD). The third non-responder (NR) was a girl with stage III disease that was refractory to chemotherapy. After MIBG treatment her tumour was surgically excised; histological examination revealed a ganglioneuroma, although the catecholamine pattern had indicated a neuroblastoma. The median survival in all patients was 129 days after the beginning of MIBG treatment (range, 55–399 days). In all patients with fever and severe bone pain, we observed rapid relief of pain and normalization of body temperature.

Table 3. Patient characteristics and outcome

Patients	Catecholamines in urine	Tumor localization by MIBG scan	Result	Follow-up
C.E.	Elevated	AM, SL, BM, LN[a]	NC[b]	120[c]
T.T.	Elevated	Pleura, SL, BM, LN	NC	55
H.S.	Elevated	SL, BM	PR	249
I.H.	Elevated	AM, SL, BM	CR	350
J.C.	Elevated	AM, SL, BM	PR	129
C.A.	Normal	AM	NR	188
J.E.	Elevated	AM, SL, BM	CR	70
M.G.	Elevated	Liver, Pleura, SL, BM, LN	NC[d]	399
N.M.	Elevated	AM	NR	365
U.A.	Elevated	AM, SL, BM	NR	120

[a] AM, abdominal mass; SL, skeletal lesion; BM, bone marrow involvement; LN, lymph node involvement
[b] NC, no change after MIBG treatment, but also no progression for a definite time period; CR, complete remission; PR, partial remission; NR, no response
[c] Patient was observed until his death
[d] Patient was lost to follow-up

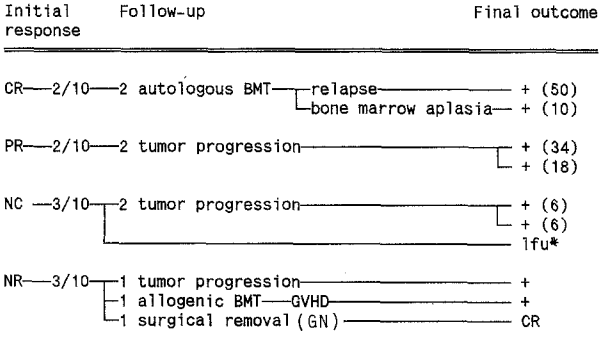

Fig. 1. Results of treatment with MIBG. The duration of continuous remission (in weeks) or lack of tumour progression after the beginning of treatment is shown *in parentheses.* An *asterisk* indicates one patient lost to follow-up. +, death; *NC*, no change after MIBG treatment, but also no progression for a definite period; *GN*, histological ganglioneuroma

[2] The remission criteria are in line with those of Berthold, given in the GPO study protocol NB 85

Table 4. Side effects observed in the haematopoietic system (by maximal grade per course; 14 evaluable course)

WHO grade	0	1	2	3	4
Haemoglobin (g/dl)	>11	9.5–10.9	8.0–9.4	6.5–7.9	<6.5
	–	5	7	2	–
Leukocytes (1,000/mm³)	>4	3.0–3.9	2.0–2.9	1.0–1.9	<0.5
	–	1	6	5	1
Thrombocytes (1,000/mm³)	>100	75–99	50–74	25–49	<25
	3	1	5	3	2

Table 7. Cumulative urinary excretion of [^{131}I]-MIBG and ^{131}I as a percentage of the delivered dose. Mean and SD were not calculated for 24- and 48-h values due to different schedules

Patient (cycle)	[^{131}I]-MIBG			^{131}I		
	24-h	48-h	6-day	24-h	48-h	6-day
M.G. (1)	22.6%	54.7%	69.3%	4.6%	10.2%	14.4%
M.G. (2)	20.2%	45.6%	60.3%	2.8%	6.2%	9.8%
J.E. (1)	30.7%	57.4%	72.8%	6.2%	10.9%	12.8%
J.E. (2)	19.1%	43.5%	59.5%	5.2%	9.6%	12.9%
I.H. (5)	32.6%	40.6%	54.9%	6.5%	7.2%	8.5%
A.K. (1)	52.4%	77.4%	94.8%	9.1%	13.6%	15.0%
N.M. (1)	52.2%	70.9%	85.8%	5.7%	7.3%	8.2%
Mean ± SD		71.1% ± 13.6%			11.7% ± 2.6%	

Side effects

The maximal MIBG dose was limited by reversible bone marrow toxicity. As shown in Table 4, leukopenia and thrombopenia occurred to varying extents, but therapy was primarily limited by effects on the platelet system. After four to five cycles a critical level of thrombopenia was reached. However, in no case was bleeding a complication. Leukopenia was generally less pronounced than after chemotherapy. It must be borne in mind that all children had previously undergone intensive treatment. Some patients briefly suffered from nausea on the 2nd or 3rd day after MIBG. Side effects involving blood pressure or the hormone systems were not observed. There was no increase in liver enzyme levels or decrease in liver function parameters (except in one case), despite sizable doses.

Pharmacological results

Pharmacological studies were carried out to determine the distribution, elimination and metabolism of MIBG. At the start of intravenous infusion, we found that MIBG ac-

Table 5. Parmacokinetic parameters (effective half-lives) of MIBG

Patient (Cycle)	Maximal concentration (kBq/ml)	Terminal half-life (h)	3. comp. (l/m²)	V_{SS} (l/m²)	MTT (h)	AUC (kBq · h/ml)	Clearance total (ml/min per m²)	Renal (ml/min per m²)
M.G. (1)	40.5	72	212	241	42	1,579	95	56
M.G. (2)	121.1	31	486	578	23	360	420	280
J.E. (1)	45.5	31	86	166	21	1,719	132	88
J.E. (2)	29.7	24	182	248	21	1,047	194	104
I.H. (5)	37.7	29	154	169	20	1,347	143	69
A.K. (1)	12.0	22	180	206	19	904	164	149
N.H. (1)	29.6	51	323	538	52	682	172	178
Mean		37.0	232	307	28	1,091	189	132
SD		16.5	123	162	12	453	99	72

V_{SS}, steady-state volume of distribution; MTT, mean transit time; AUC, area under the curve

Table 6. Parmacokinetic parameters (effective half-lives) of ^{131}I

Patient (Cycle)	Maximal concentration (kBq/ml)	Terminal half-life (h)	3. comp. (l/m²)	V_{SS} (l/m²)	MTT (h)	AUC (kBq · h/l)	Clearance total (ml/min per m²)	Renal (ml/min per m²)
M.G. (1)	26.2	48.5	156	164	39	1,079	70	16
M.G. (2)	46.1	68.6	302	337	69	818	81	21
J.E. (1)	46.3	120.1	156	194	47	1,952	68	16
J.E. (2)	44.3	87.0	206	272	62	1,366	74	22
I.H. (5)	24.7	50.4	68	69	19	3,183	60	4
A.K. (1)	32.2	96.1	106	121	51	1,797	40	14
N.H. (1)	32.6	30.3	68	172	29	562	98	18
Mean		71.6	152	190	45	1,537	70	16
SD		29.0	77	83	16	816	17	5

V_{SS}, steady-state volume of distribution; MTT, mean transit time; AUC, area under the curve

counted for 93.0%±2.3% (n = 10) of the total radioactivity; at the end of the infusion it made up 88.0%±7.4%. The non-MIBG radioactivity was predominantly attributable to ^{131}I, which amounted to 5.5%±1.8% before and 10.3%±6.9% after the infusion. These differences were significant according to the Wilcoxon test ($P < 0.003$).

Stability examinations were carried out in ten infusion courses, one of which involved a 24-h infusion and the other nine, were 4-h infusions. In the patient who received the 24-h infusion, 88.1% of the measured radioactivity was attributable to MIBG before the infusion, which decreased to 82.4% after the infusion; the non-MIBG radioactivity amounted to 8.4% of the total before and 15.4% after the infusion. The range of the values for 4-h infusions was 88.8%–95.9% before and 68.2%–93.7% after infusion for MIBG, and 4.2%–9.7% before and 4.5%–28.8% afterward for non-MIBG activity. The values in the patient who had a 24-h infusion were therefore within the range of those in patients who received 4-h infusions.

The pharmacokinetic parameters can be described by a three-compartment model. The following parameters (effective half-lives) for MIBG (Table 5) were determined: mean terminal half-life (37.6 h), volume of distribution (307 l/m^2), and an AUC value (1091.1 kBq·h/ml). The total body clearance was 189.9 ml/min per m^2. The values for ^{131}I are shown in Table 6. The percentage of ^{131}I excreted in urine (Table 7) did not significantly differ from that measured during infusion, which indicates that deiodinization is not a major metabolic pathway for MIBG. Due to its longer half-life, the radioactivity-time product of ^{131}I was higher than that of intact MIBG.

Results of dosimetric measurements

For our 10 patients the doses used in 14 therapy courses were calculated using the MIRD programme. The following mean values were obtained: liver, 540 µGy/MBq; whole body, 160 µGy/MBq; and tumour, 10,500 µGy/MBq. With a mean total radioactivity of 4,219 MBq/course, a mean liver dose of 2.3 Gy/course, a mean total body dose of 0.67 Gy/course and a mean tumour dose of 44.3 Gy/course were achieved. Nevertheless, we observed distinctly higher levels in the liver as well as in the whole body in different age groups. There was no correlation between injected MIBG and doses calculated for either the tumour or the other sites (Table 8). We also found no correlation between the radiation doses targeted for the main tumour sites and the efficacy of the therapy as a whole.

Table 8. Radiation doses in four patients (after seven courses) with complete, evaluable data

Patient	Activity (GBq)	Calculated dose (cGy)		
		Liver	BM	Tumor
J.E.	6.7	380	130	9,000
	6.2	240	79	3,000
J.C.	3.7	190	67	7,400
	2.2	100	28	3,300
M.G.	8.9	130	61	2,300
	7.0	190	93	6,900
I.H.	1.9	38	24	1,600

Discussion

The main problem in cancer therapy is trying to treat malignant tissue without disturbing the normal function of healthy tissue. Efforts to find an effective agent or therapeutic procedure to influence only the tumour have been unsuccessful. Monoclonal antibodies show promise, but as yet they have fallen short of expectations.

Another approach has been to use drugs linked to radioactive isotopes that can be taken up by tumour tissue. Such a drug is benzylguanidine, which is selective for the sympathetic nerve tissue that becomes malignant in the case of neuroblastoma. Kimmig et al. [9] and our group [16] first showed that this drug can be used in scintigraphic imaging of neuroblastoma when it is labelled with radioactive iodine. As a result, our group drew up the first treatment protocol for use of this labelled drug [10]. In our previous report on six patients [17], we discussed the therapeutic value of this new method. The current results confirm the previous data and experiences of other groups [14, 19]. The French group [7] reported only 2 objective responses in 12 patients and suggested that tumour heterogeneity may explain these disappointing results in the face of rather high tumour doses.

A recent report by Voute et al. [20] showed 5 complete remissions after 22 otherwise comparable patients were treated with this drug. Whereas it is possible to attain complete remissions, efforts to achieve a complete cure using this substance have failed, although Voute's patients [20] who achieved complete remissions were still living at the time of publication. More often, partial remissions or an arrest of the disease resulted.

Where some success was achieved, i.e. where there was either a CR or PR, no difference between effects on the primary tumour and those on the metastases could be detected. At the beginning of the present study, we thought that allogeneic BMT might improve chances for a cure in metastatic neuroblastoma. It was therefore our aim, whenever possible, to induce a remission and then carry out a bone marrow transplantation. However, recent data on BMT in neuroblastoma are disappointing [2, 13], with no striking increase in long-term survival. Nevertheless, autologous BMT does result in longer survival and requires less hospitalization than equivalent chemotherapy [13]. Because some patients additionally underwent BMT, the duration of the MIBG-induced remission is difficult to evaluate. The comparative benefits of the different regimens cannot yet be satisfactorily assessed.

Measurements of MIBG's stability showed that correct handling of the substance (which is supplied frozen) ensures 95% MIBG-bound iodine, as guaranteed by the producer. After only 4 h infusion, the proportion of MIBG-bound iodine decreased to 88%, whereas the proportion of free iodine increased to about 10% (due to autoradiolysis and, possibly, other events not yet investigated). Pharmacological studies showed that free radioactive iodine has a very long half-life compared with MIBG-bound iodine. Consequently, the radioactivity-time product of free iodine is about 50% higher than that of MIBG-bound iodine. This means that free iodine may be responsible for a higher extent of whole-body and liver toxicity, despite the fact that it amounts to only 10% of the infusion solution. Thus, to minimize this non-specific radiotoxicity, a way must be found to minimize the amount of free iodine in the infusion solution.

The tumour doses computed by the MIRD programme were not easy to interpret. Certain amounts of injected radioactivity resulted in quite different tumour doses. In addition, similar tumour doses provoked very different clinical responses (also see Hartmann et al. [7]). Both of these observations may reflect the heterogeneity of neuroblastoma tissue. From tissue cells can very rapidly lose their capacity to take up and store MIBG [3].

The present experience with MIBG allows a few conclusions to be drawn. MIBG appears to be a fairly effective substance in treating neuroblastoma, but its optimal use in therapy has not yet been determined. A clinical study should be conducted in which MIBG, as the initial therapeutic agent, is used before the tumour cells lose their ability to take up this substance.

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