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Oral (*E*)-5-(2-Bromovinyl)-2′-Deoxyuridine Treatment of Severe Herpes zoster in Cancer Patients

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Abstract—*BVDU [(E)-5-(2-bromovinyl)-2′-deoxyuridine] is a highly potent and selective anti-herpes drug. It is particularly active against Varicella zoster virus, as demonstrated in cell culture and animals (monkeys). BVDU has been administered orally, at a dose of* 7.5 mg/kg/day *for* 5 days, *to* 20 *patients with severe localised or disseminated Herpes zoster. All patients had a malignant disorder for which they had been given intensive chemo- or radiotherapy. Upon BVDU treatment a rapid cessation of the acute Herpes zoster episode was noted in all but one patient. In the majority of patients progression of the infection was arrested within* 1 day *of starting treatment. No toxic side-effects could be attributed to the drug at the dosage used.*

INTRODUCTION

BVDU [(*E*)-5-(2-bromovinyl)-2′-deoxyuridine] is one of the most potent and selective anti-herpes agents described to date. It is particularly active against Herpes simplex virus type 1 (HSV-1) and Varicella zoster virus (VZV). In cell culture BVDU inhibits the replication of these viruses at a concentration ranging from 0.002 to 0.01 μg/ml [1–4]. BVDU does not affect normal cell metabolism at concentrations up to 50–100 μg/ml, thus achieving a selectivity index (ratio of toxic dose to antiviral dose) of at an average 10,000.

The selectivity of BDVU as an anti-herpes agent is based upon a specific phosphorylation by the virus-induced deoxythymidine (dThd) kinase, which restricts the further action of BVDU to the virus-infected cells [5, 6]. After it has been converted to its 5′-triphosphate, BVDU competes with dThd 5′-triphosphate for incorporation into DNA [7], and thereby inhibits viral DNA polymerase to a greater extent than cellular DNA polymerases [8]. BVDU is specifically incorporated into viral DNA, and this incorporation may well explain the antiviral activity of the compound [9].

BVDU has been the subject of a wide variety of animal studies that have demonstrated the efficacy of the compound in the topical and systemic, i.e. oral, treatment of cutaneous HSV-1 infections in athymic nude mice [10], orofacial HSV-1 infections in hairless mice [11], herpetic eye infections in rabbits [12–14] and herpetic encephalitis in mice [15, 16]. At a dose of 5, 10 or 15 mg/kg/day administered by the oral, intramuscular or intravenous route BVDU has proven efficacious in suppressing all manifestations of simian Varicella virus infection in African green monkeys [17].

Simian Varicella is reminiscent of generalized VZV infection in humans. Prompted by the efficacy of oral BVDU in the simian Varicella virus model and its apparent freedom of toxicity, we have embarked upon clinical pilot studies with BVDU in the treatment of VZV infections in humans. This report describes our clinical experience with oral BVDU in the treatment of 20 patients with severe localised or disseminated Herpes zoster. All patients had been given intensive chemotherapy or radiotherapy, or both, for an underlying malignant disorder. A preliminary account on oral BVDU treatment of Herpes zoster has been published previously [18].

MATERIALS AND METHODS

All patients had been treated for a malignant disorder and presented with an intercurrent

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Herpes zoster infection. They did not receive any antiviral treatment other than BVDU. BVDU was administered orally as capsules of 125 mg. Patients with body weight between 50 and 70 kg received 125 mg BVDU t.i.d.; patients with body weight higher than 70 kg received 125 mg BVDU q.i.d. (approximately 7.5 mg/kg body weight). Informed consent to treatment was obtained from all patients.

The patients were examined daily during treatment, and at regular intervals afterwards, to evaluate pain and fever, and duration, evolution and extension of the lesions. Complete blood count (with reticulocytes and platelets), urea, creatinine, serum transaminases (glutamic–pyruvic transaminase and glutamic–oxaloacetic transaminase) and γ-glutamic transpeptidase (γ-GT) were measured on the first, third and fifth days of treatment.

The characteristics of the patients are presented in Table 1. There were 8 males and 12 females. Their mean age was 48.5 yr (16–70 yr). All the patients had one or more underlying malignant disease. Five patients had Hodgkin's disease, three non-Hodgkin's lymphoma, five breast cancer, two chronic lymphocytic leukaemia, one chronic myelocytic leukaemia, one ovarian carcinoma, one ovarian teratocarcinoma, one prostate cancer, one bronchus carcinoma, one malignant melanoma and one epithelioma of the larynx and skin. Two patients had more than one malignant disease: patient No. 1 had chronic lymphocytic leukaemia and epithelioma of the larynx and skin, and patient No. 10 had non-Hodgkin's lymphoma and breast cancer. Most patients had a long history of malignant disease. The treatment for malignant disease was started 3–226 months (mean 50.5 months) before the Herpes zoster episode occurred. Three patients had a disseminated zoster infection, thirteen had a localised zoster infection and four had a localised zoster infection with dissemination. One patient developed the clinical signs of encephalitis.

The treatment the patients received for their underlying disorder and the presentation form of the Herpes zoster infection are listed in Table 2. Seventeen patients had received or were receiving intensive cytostatic chemotherapy when the Herpes zoster infection occurred. Sixteen patients had received radiotherapy; four of them were actually treated with radiotherapy when the Herpes zoster infection occurred. Fifteen patients had received both radiotherapy and cytostatic chemotherapy. Four patients had only received

Table 1. Patient characteristics

Case No.		Patient age (yr)	Sex	Underlying disorder	Duration of malignant disease (months)	Herpes zoster infection
1	RJ	70	M	chronic lymphocytic leukemia epithelioma of larynx and skin	60	localised
2	MO	46	F	breast cancer	45	localised
3	HC	62	F	breast cancer	226	localised
4	PJ	48	M	non-Hodgkin's lymphoma	69	localised and disseminated
5	KR	28	M	Hodgkin's disease	17	localised
6	VJ	32	M	Hodgkin's disease	109	localised and disseminated
7	BJ	52	M	Hodgkin's disease	8	localised
8	DH	42	F	Hodgkin's disease	151	localised
9	VH	16	F	ovarian teratocarcinoma	33	localised, disseminated and encephalitis
10	VM	51	F	non-Hodgkin's lymphoma (breast cancer 4 yr before)	7	localised and disseminated
11	VG	42	F	malignant melanoma	3	localised
12	DM	64	F	ovarian carcinoma	14	localised
13	VS	33	F	chronic myelocytic leukaemia	22	disseminated
14	SA	52	F	breast cancer	57	localised
15	GA	67	F	breast cancer	70	localised
16	HA	58	M	bronchus carcinoma	9	localised
17	VL	70	M	prostate cancer	84	localised
18	BP	17	F	Hodgkin's disease	7	localised
19	WG	65	M	chronic lymphocytic leukaemia	7	disseminated
20	HM	55	F	non-Hodgkin's lymphoma	11	disseminated

Table 2. Previous treatment of the patients and presentation of the Herpes zoster infection

Case No.		Chemotherapy	Radiotherapy field (terminated . . . months before onset of Herpes zoster infection)		Localisation of Herpes zoster lesions
1	RJ	chlorambucil	larynx		thoracic
2	MO	cyclophosphamide-vincristine-methotrexate-fluorouracil-adriamycin	thorax-subclavia	44	thoracic
3	HC	VAC-testolactone-tamoxifen	sacrum	42	cranial
4	PJ	CVP	cervical	2	cervical and disseminated
5	KR	ABVD-MOPP	mantle field	9	cervical
6	VJ	MOPP	mantle field	84	right leg and disseminated
7	BJ		during total nodal irradiation		cervical
8	DH	MOPP-ABVD	inverted Y	108	cervical
9	VH	VAC			cranial and disseminated
10	VM	CVP	abdominal, pelvic, inguinal	5	sacral and disseminated
11	VG	lomustine-bleomycin-vincristine-dacarbazine	cranial	2	cranial
12	DM	adriamycin-cyclophosphamide-*cis*-platinum-etoposide	abdomen	1	sacral
13	VS	hydroxyurea			disseminated
14	SA		breast, thorax, subclavia		lumbosacral
15	GA	melphalan	thoracal vertebrae	1	thoracic
16	HA	OCA-hexamethylmelamine-etoposide	thorax skull	8 7	thoracic
17	VL	oestrogens	pelvis	12	abdominal
18	BP	MOPP-ABVD	mantle field	1 week	sacral
19	WG	chorambucil-vincristine-prednisone			disseminated
20	HM	adriamycin-cyclophosphamide-epipodophyllotoxine-prednisone-vincristine			disseminated

*MOPP: mustine-oncovin-procarbazine-prednisone; ABVD: adriamycin-bleomycin-vinblastine-dacarbazine; CVP: cyclophosphamide-vincristine-prednisone; VAC: vincristine-actinomycin D-cyclophosphamide; OCA: oncovin-cyclophosphamide-adriamycin.

cytostatic chemotherapy and one patient only hormonal treatment and radiotherapy. It is noteworthy that the localisation of the zoster lesions corresponded closely to the irradiated areas (case Nos 2, 4, 5, 7, 10, 11, 12, 15, 16 and 17).

RESULTS

The observations before, during and after oral BVDU treatment are presented in Table 3. The duration of the lesions before the start of oral BVDU treatment ranged from 0 to 41 days (mean 5.5 days). Two patients (case Nos 19 and 20) had been treated unsuccessfully with acyclovir for 5 days before they were switched to BVDU treatment.

Only two patients had fever when BVDU treatment was started. In patient No. 10 the fever continued until day 11, when the patient died from progressive lymphoma. In patient No. 12 the fever resolved on day 5 of BVDU treatment.

The development of new vesicular lesions was followed in 19 patients. In 18 patients formation of new lesions was arrested within 1–5 days (mean 1.83 days). In 12 patients new lesions ceased to appear within 1 day of starting treatment. In only one patient (No. 10) did new lesions continue to appear despite BVDU treatment.

Three weeks after the start of BVDU treatment, the lesions had completely disappeared in 11 patients. Two patients (Nos 1 and 8) were lost for follow-up at this time. Pain had disappeared completely in nine patients at 3 weeks after BVDU treatment. In three patient severe post-herpetic neuralgia was experienced at this time. In one patient (No. 2) the pain disappeared during BVDU therapy but resumed after cessation of the therapy.

According to their response to BVDU treatment, the patients could be divided into four categories, as shown in Table 4. Only one patient (No. 10) could be regarded as a treatment failure.

The mean follow-up time has been 11.3 months

Table 3. Observations before, during and after oral BVDU treatment

Case No.	Duration of lesions before BVDU treatment (days)	During treatment: Fever resolved within *n* days	During treatment: No new lesions appeared from day *x* onwards	Situation at 3 weeks after treatment	Follow-up (months)
1 RJ	0	no fever	unknown	unknown	10
2 MO	1	no fever	1	pain increased after cessation of BVDU treatment, lesions disappeared	2
3 HC	3	no fever	1	complete disappearance of pain and lesions	22
4 PJ	7	no fever	3	complete disappearance of pain and lesions	23
5 KR	3	no fever	4	complete disappearance of pain and lesions	10
6 VJ	2	no fever	1	complete disappearance of pain and lesions	27
7 BJ	2	no fever	5	lesions almost completely disappeared; severe post-herpetic neuralgia	25
8 DH	1	no fever	1	crusting; severe post-herpetic neuralgia	25
9 VH	5	no fever	3	complete disappearance of pain and lesions	24
10 VM	2	continuous fever	10	progressive disease (died after 11 days)	11 days
11 VG	1	no fever	1	lesions disappeared; severe post-herpetic neuralgia	2
12 DM	4	5	1	post-herpetic neuralgia; slow healing	2
13 VS	2	no fever	1	complete disappearance of pain and lesions	5
14 SA	1	no fever	1	complete disappearance of pain and lesions	12
15 GA	14	no fever	1	post-herpetic neuralgia; crusts	12
16 HA	1	no fever	3	complete disappearance of pain and lesions	8
17 VL	5	no fever	3	scars; pain decreased	9
18 BP	4	no fever	1	unknown	2
19 WG	11 (after failure of acyclovir therapy)	no fever	1	crusting	4
20 HM	41 (after failure of acyclovir therapy)	no fever	1	complete disappearance of pain and lesions	2

Table 4. Evaluation of clinical response of Herpes zoster infection to oral BVDU treatment

		No. of patients (18/20)*
1. Excellent:	rapid cessation of new lesion formation and pain; rapid crusting and healing	9/18 (case Nos 3–6, 9, 13, 14, 16, 20)
2. Good:	rapid cessation of new lesion formation; pain relief not necessarily complete	3/18 (case Nos 2, 17, 19)
3. Moderate:	long (more than 14 days) healing time; post-herpetic neuralgia	5/18 (case Nos 7, 8, 11, 12, 15)
4. Poor:	little or no clinical response to BVDU therapy; appearance of lesions during therapy, delay or absence of crusting or healing, or severe pain with no relief during treatment	1/18 (case No. 10)

*For 2 patients (Nos 1 and 18) the data were insufficient to allow a definitive conclusion.

(range: 0–27 months). No recurrence of Herpes zoster has occurred in any of the patients treated with BVDU. Twelve of the 20 patients have meanwhile died from progressive malignant disease.

BVDU was well tolerated in all 20 patients. Patient No. 2 experienced vomiting 5 hr after taking, in error, the first day's medication as one dose instead of three divided doses. This gastrointestinal disturbance persisted for about 8 hr, but was not sufficiently severe to cease therapy. Patient No. 1 developed a gastric haemorrhage 1 week after cessation of BVDU therapy. This patient was suffering from a gastric ulcer and had

had gastric haemorrhages prior to BVDU treatment. Therefore, it is unlikely that his gastric haemorrhage resulted from BVDU therapy.

Except for a mild macrocytosis in two patients and a transitory rise in blood urea and creatinine on the last day of BVDU treatment in one patient (which may or may not be related to BVDU therapy), all haematological and biochemical blood parameters remained unchanged during BVDU treatment. Hence at the dosage regimen used there was no evidence of drug toxicity for bone marrow, liver, kidney or any other organ.

DISCUSSION

Herpes zoster is a common infection in immunocompromised patients, especially in those with lymphoproliferative neoplasia. Herpes zoster infections are clearly in need of an effective treatment. The antiviral drugs that have so far been evaluated in the treatment of acute Herpes zoster include interferon [19, 20], vidarabine [21, 22] and acyclovir [23–26]. Although these agents have been shown to shorten the duration of the disease and/or to reduce the danger of visceral dissemination, the results are all but overwhelming. An additional impediment is that all three drugs have to be administered parenterally, vidarabine and acyclovir even intravenously, to accomplish their beneficial effects.

As compared to vidarabine and acyclovir, BVDU offers a number of interesting perspectives that make it a more attractive candidate for the systemic treatment of Herpes zoster infections: (i) BVDU is intrinsically much more potent against VZV than either acyclovir or vidarabine: the 50% inhibitory dose for ten different VZV strains in cell culture is 0.0024, 4.64 and 1.62 μg/ml for BVDU, acyclovir and vidarabine, respectively [4]; (ii) BVDU can be administered orally whereas acyclovir and vidarabine must be given intravenously to achieve sufficiently high blood drug levels; and (iii) under conditions where vidarabine is ineffective [27] and acyclovir marginally effective [28], BVDU has a dramatic suppressive effect on all manifestations of simian Varicella virus infection [17], a laboratory model that is closely related to generalized VZV infection in humans.

This study was conceived as an open clinical trial to determine the safety and efficacy of BVDU in the oral treatment of Herpes zoster infections in immunocompromised patients. At the dosage regimen used (7.5 mg/kg/day, divided over 3 or 4 doses per day) BVDU caused a prompt cessation of the acute zoster episode in all but one patient. In 60% of patients the disease was even arrested after 1 day of BVDU treatment. The one patient who did not respond to BVDU therapy died shortly thereafter from his underlying lymphoproliferative neoplasia. Remarkably, two patients who failed to respond to acyclovir therapy recovered from their Herpes zoster infection within 1 day of BVDU treatment. No toxic side-effects were observed that could be attributed to the drug and recurrences of zoster were not seen in any of the patients treated with BVDU and followed for a period up to 27 months.

Considering the pitfalls inherently linked to open clinical studies, it is mandatory to submit BVDU to carefully controlled double-blind, and preferably multicentred, trials before its value in the treatment of Herpes zoster can be unequivocally assessed. The high potency of BVDU against VZV in cell cultures [3, 4], its efficacy against simian Varicella virus infection in monkeys [17], and the initial clinical results presented here appear such that BVDU is likely to prove a valuable drug in the treatment of Varicella and Herpes zoster infections.

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