Cytosine arabinoside treatment of varicella-zoster

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SOME patients with impaired host responses may develop life-threatening infections with varicella-zoster (VZ) and other herpes viruses. Among the conditions which can predispose to severe infections with these agents are malignancies, especially those of the reticuloendothelial system,¹⁻¹² or the neonatal state, or therapy with antitumour agents which are coincidentally immuno-suppressive.¹³⁻¹⁵ Severe disseminated varicella has also been seen in renal transplant patients.¹⁶ In addition, severe infections may be found in those diseases which prevent naturally occurring deficiencies of delayed hypersensitivity, such as congenital disorders of thymic function,^{17,18} starvation¹⁹ and advanced age.²⁰

No consistently effective form of antiviral therapy for disseminated varicella-zoster existed prior to the introduction of cytosine arabinoside (cytarabine).²¹⁻²⁵ Other DNA virus diseases such as herpes simplex keratitis,²⁶ whitlow,²⁷ and encephalitis²⁸ have been reported as showing ameliorated courses when treated topically or systemically with idoxo-deoxyuridine (IUdR), another pyrimidine antimetabolite. However, this drug may be less effective topically against varicella,²⁹ as well as extensively dehalogenated *in vivo*.³⁰

Over the past 4 years we have treated sixteen adult patients and four children with disseminated varicella and zoster using cytarabine, including two with post-herpetic pain from zoster, with encouraging results in most. In addition, we have treated three patients

with neonatal disseminated herpes simplex infection with IUdR with good results.

Clinical material

The adult patients (Table 1) were of two types, those on immunosuppressive therapy for malignancy or renal transplant maintenance and patients with localized herpes zoster without obvious predisposing factors. In the latter group we see a predominance of traditional localized herpes zoster, restricted to one or few dermatomes. The more localized distribution observed in this group probably represents less impairment of immunologic competency. There was a predominance of malignancies of the lymphatic system. Such malignancies constitute a minority of the patients with advanced malignancy requiring chemotherapy. Nevertheless, they are commonly both accompanied by more immunologic defects than have been reported for other malignancies, and are more commonly treated by immunosuppressive agents, such as cyclophosphamide, prednisone and vinca alkaloids, than the more common solid tumours such as breast and colon. The latter are apt to be treated with relatively nonimmunosuppressive agents such as 5-fluorouracil and the sex hormones.

The paediatric oncologic patients were three in number (Table 2), two with acute lymphoblastic leukemia and one with reticulum cell sarcoma. The lymphoblastic variety of leukemia has been considered more likely to arise from a derangement in the lympho-immune apparatus than the myelogenous variety, and the incidence of varicella in lymphoblastic leukemia is 4%, while in acute myeloblastic

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TABLE 1. Adult patients

No.	Initials	Age	Sex	Underlying disease	Disease extent			Treatment		Maximum toxicity			Other	
					Skin	Muc. mem.	Lung	Infusion duration	Dose/day	No. days	WBC (×10 ³ /mm ³)	Day		Response
1	A.G.	40	F	Lymphosarcoma (a) (b)	+	0	0	24 hr	100	2	0		+	Relapsed
					+	0	0	24 hr	100	4	0		+	No relapse
2	J.W.	18	F	Hodgkin's	Z	0	0	24 hr	50	3	6.0→2.9	4	+	
3	D.B.	19	M	Hodgkin's	+	0	0	24 hr	100	5	0		+	
4	R.M.	35	M	Hodgkin's	Z	0	0	2 hr	50	5	0		+	Patient died day 8
5	T.A.	26	M	Hodgkin's	+	+		8 hr	100-200	7	13.4→5.4	7	+	
6	R.R.	66	M	LSA	Z	0	0	Direct	200	3	5.6→3.4	2	+	
7	M.D.N.		F	Ca. breast on cyclophosphamide	Z	0	0	SC	80	3	0		+	
8	R.A.	46	M	Renal transplant	+	0	0	24 hr	100					3uHIP*
9	K.G.	91	F	None	Z	0	0	4 hr	50	4	5.4-4.5	4	+	
10	N.H.	70	F	(a) None	Z	0	0	8 hr	25	3	5.0-3.7	3	+	1uHIP
			(b) Residual zoster pain	0	0	0	8 hr	50	7	0	0		0	
11	G.N.	57	M	Residual zoster pain	0	0	0	8 hr	30	4	5.6-5.0	3	0	
12	P.D.	70	M	None	Z	0	+	24 hr	175	6	7.0-0.7 Plates. 195,000 →6000	15	+	Thought to have zoster encephalitis
												13		Required 15 platelet and 3 blood transfusions
13	G.T.	56	M	None	Z	0	0	8 hr	100	4	5.9→3.6	3	+	Thought to involve geniculate, otic ganglia
14	G.B.	70	M	None	Z	0	0	24 hr	92	4	6.9→4.7	7	+	
15	A.S.	78	F	None	Z	0	0	SC	50	4	0		+	
16	J.R.	49	F	None	Z	0	0	4 hr	40	3	0		+	

*HIP, human immune plasma.

TABLE 2. Paediatric patients with varicella-zoster

Case no.	Initials	Sex	Age (years)	Underlying disease	Previous immuno-suppressive Rx	Extent of disease, drug administration								Response	Comments	
						Skin	Muc. mem.	Lung	CNS	Route	Hrs/ day	Total dose/ day (mg)	No. days			Maximum toxicity
1	A.P.	M	8½	Nephrotic syndrome	Prednisone	+		+	0	i.v.	24	25-50	7	0	+	
2	C.H.	F		Acute lymphoblastic leukemia	Prednisone, l-asparaginase	+	0	0	0	i.v.	24	92	3	2.1→0.9	+	Max. toxicity on day
3	R.V.	F	3½	Acute lymphoblastic leukemia		+		+		i.v.	24	65	<1	0	0	Died less than 24 hr
4	L.D.P.	M	12½	Reticulum cell sarcoma	Prednisone, Vincristine, Procarbazine, cyclophosphamide	Z*	+	0	0	i.v.	24	100	2½	0	+	Had received zoster immune serum without effect

*Z, localized to one or a few dermatomes with previous history of varicella.

leukemia it is less than 1 in 300.³¹ The other child was receiving prednisone for nephrotic syndrome.

It will be most interesting to observe whether the current regimens for cancer chemotherapy which contain non-specific immunologic stimulants, such as BCG, will result in a greater resistance to varicella-zoster virus. Most of the patients were in the later stages of their disease, and had been treated with a number of other immunosuppressive agents over several years, with a possibly cumulative immunosuppressive effect. There was a random distribution of sex and ages.

Cytarabine ('Cytosar' by Upjohn Co., Kalamazoo, Michigan) was given intravenously in dextrose and water or normal saline over the specified periods. Idoxuridine (Calbiochem, Los Angeles, California) was given intravenously in dextrose and water or normal saline over the specified periods. The diagnosis of varicella-zoster was made on clinical grounds and virologic studies were not usually obtained. In all patients, there was evidence of progression of disease with new crops of vesicles appearing and without crusting of any lesion. All herpes simplex patients had a positive virologic diagnosis made prior to the institution of therapy.

Results

Varicella-zoster (Table 3)

One adult patient, R.M., had extensive zoster ophthalmicus with gangrene of the scalp, and although the lesions appeared to dry up, he expired from sepsis before a definite evaluation of therapy could be made. Two adult patients were treated for post-zoster pain in the absence of active disease, but without benefit. The other patients showed uniform objective improvement in their eruptions following therapy. This appeared to be relatively independent of the duration of the infusions and over the range of doses used (Table 4). The toxicity observed was confined to the bone marrow, and affected primarily the white cells. It was mild even in patients with

TABLE 3. Therapy of herpes viruses

Total number of cases	23
Excluded because of early death	1
Adequate therapy	22
Types of infection	
Neonatal herpes simplex	3
Disseminated varicella	7
Localized zoster	12
Zoster pain	2
Underlying diseases	
Malignant	10
Immunosuppressed	2
None	8
Neonatal	3
Responses	
Good	22/23
Relapses	2
Pain only	0/2

initial leukopenia from disease or previous therapy. Recovery of white counts, and platelets on the few occasions when they were slightly depressed, was rapid upon cessation of cytarabine therapy. In two cases relapses were noted, in both instances re-institution of therapy succeeded. Most patients had no recurrences, suggesting a degree of retained immunocompetence. Failure of later antibody response to V-Z virus is not a feature of the severe infections observed in patients with malignancy. No delayed untoward drug effects have been observed, although the periods of observation were limited by the natural progression of neoplasms in most of the patients. Hence the immunosuppressive effects of cytarabine itself do not appear important in this therapeutic situation.³²

Herpes simplex encephalitis

These neonates (Table 5) were all in extremis at the time of onset of therapy. Beneficial results were noted promptly, usually in 48–72 hr in all, in respect to skin lesions and seizure patterns. Two were treated by constant infusions, as were used in our first case,²⁸ and one with large doses given q12 hr to

TABLE 4. Drug infusion durations

Drug	Type	No. of patients	Dose (mg/m ² /day)	No. of days	No. of responses	Maximum toxicity*
Cytarabine	Direct i.v. push 2–8 hr	1	200	2	1	
		5	15–40	3, 4, 5, 7	5	1+
	24 hr	2	100	3, 7	2	1+
		2	50	3	2	1+
		7	100	1–7	7	3+ (1 patient)
		1	175	7	1	4+
		3	100		3	0
IUdR	Continuous	1	1100	5	1	alopecia
	Direct i.v.					

*Toxicity defined as: 1+, fall of up to 2000 and 3000 in WBC, or to final values of 3000; 2+, fall of between 2000 and 3000 in WBC, or to final values of 3000; 3+, fall of WBC to less than 2000; 4+, fall of WBC and platelets to less than 2000 and 75,000, need for transfusion; 5+, fatal.

TABLE 5. Neonatal herpes samples treated with idoxuridine

Case no.	Initials	Sex	Age	Underlying disease	Extent of disease				Drug administration, duration					Day	Response	Comments
					Skin	Muc.			Route	Hr/day	Total Dose/ day (mg)	No. days				
						Mem.	Lung	CNS								
1	M.N.	M	12 days	0	+			+	i.v.	24	100	5	WBC 11.8→5.8	6	Good	+ive culture
1	M.N.	M	30 days	0				+	i.v.	24	100	5	0		Good	+ive culture
2	W.W.	M	13 days	0	+	+	+	+	i.v.	24	125	5	WBC 7.6→5.0 Plats. 2,620,000 →23,000	10		No clinical bleeding
3	F.C.M.	M	56 days	Hydrocephalus, ventricular shunt	+	+		+	i.v.	8½	1100	5	0	10	Good	+ive culture Alopecia

a total dose which was 10 times that received by the others. In none of the patients was significant bone marrow or gastrointestinal toxicity noted, however the patient receiving the high 'pulse' doses developed total alopecia several weeks later, which gradually disappeared.

Discussion

The incidence of localized herpes zoster infections, as reported in the general population over 50-years-old,³³ is similar to that in patients with Hodgkin's disease,^{1, 2, 4, 7, 8, 11, 12}, hematological neoplasms^{3-6, 10} or renal transplants,¹⁶ but the dissemination of herpes zoster occurs with greater frequency in patients with an underlying disease.³⁴ When dissemination occurs, it is most frequently within the first week of illness. The healing of disseminated varicella-zoster can be very slow, complicated by necrosis and gangrene and followed by skin scarring, and mortality can reach 33%.

In adults, varicella pneumonia³⁵⁻⁴⁰ is common; an incidence of 16% has been reported in an Army population where every patient with chicken-pox had chest films taken. The mortality in varicella with pneumonia is 10-30%, as contrasted to less than 1% in the absence of pneumonia. The potentially lethal outcome of varicella-zoster in the situations described above has prompted sero-therapy with convalescent or 'hyperimmune' plasma or gammaglobulin and pooled γ -globulin. The results of this therapy are reported as variable, and no controlled studies have been done, hence the efficiency of plasma therapy is still to be established.⁴¹ In the present series no difference in course can be observed between the three patients who received both serotherapy and cytarabine and those who received cytarabine alone. A more prolonged interval between serotherapy and administration of cytarabine might have provided clearer evidence for the efficacy of the drug. This variable should be controlled carefully in future prospective studies.

Passive immunization with zoster-immune-globulin may reduce the frequency of clinical chicken-pox, and the appearance of complement-fixing antibodies in healthy family contacts.⁴² This promising report should stimulate further attempts to prevent varicella in high-risk groups of patients, although the reactivation of old varicella represented by herpes zoster may be difficult to prevent.

In the patients reported above, recovery from severe herpes infections was closely associated with the administration of antimetabolite therapy. Cytarabine was chosen for the treatment of V-Z because it inhibits DNA synthesis⁴³ and the *in vitro* replication of DNA viruses, including the herpes-varicella group.^{44, 45} Trifluoromethyldeoxyuridine,⁴⁶ and adenine arabinoside,⁴⁷ among other anti-

metabolites, have been shown also to inhibit this group of viruses *in vitro* and *in vivo*. IUdR is the only one of these marketed as showing effectiveness in herpes simplex, but it is extensively dehalogenated by mammalian tissues.³⁰ In addition to their clinical availability, these antimetabolites (Ara-C and IUdR) have several other theoretical advantages: they are easy to administer by multiple routes, have mild bone marrow toxicity which reverses rapidly, and are detoxified by host tissues and hence do not persist in tissues. The use of anti-DNA tumour chemotherapeutic drugs as antiviral agents also has attractive theoretical aspects: only a small fraction of tumour cells will be synthesizing DNA in one 24-hr period, while the virions are more apt to be constantly replicating, thus presenting more of a target for the drug. In addition, DNA replication (doubling) time of the virion is very short compared with even rapidly dividing normal human tissues, while tumour cells often divide inefficiently and more slowly than host tissues; as a result, a short exposure to the antimetabolite could inhibit a large fraction of replicating virions while leaving most of the normal host tissue undamaged. Viruses may induce new enzymes not present in the host, such as kinases and polymerases,⁴⁸ which may convert antimetabolites into their active forms, but only within virus-infected cells. Finally, viruses are readily recognized as 'foreign' by the host immune system, so that if the virion population could be inhibited by cytarabine (or idoxuridine), specific host immune recognition systems might be given time to react and produce infection-controlling antibodies.

The cumulative toxic effects of these drugs seen in antitumour therapy might not be encountered if short-term intense exposure of virus to the drug could be accomplished. In the initial V-Z patients, drug was given continuously over 36 hr in doses known from previous antitumour work to be relatively non-toxic. After remissions were observed with great regularity, shortening of the period of infusion and lowering the dose was undertaken (Table 4). At present it appears that 2-4 hr intravenous infusion of 25-50 mg/m² for 3-5 days will routinely control the infection, and without clinically significant white count depression even in previously myelosuppressed patients. Recently, Juel-Jensen has reported benefit from direct daily injections of low doses of cytarabine.²⁴

Spontaneous recovery from neonatal herpes simplex or from disseminated varicella-zoster might have been observed in these patients, but this seems unlikely. We feel that the evidence is strongly suggestive of a beneficial effect from cytarabine and idoxuridine. A controlled co-operative randomized clinical trial should be undertaken for both clinical conditions.

Acknowledgments

We wish to thank Dr Robert Lewis and Dr William deWys for their summaries of patient data, and Upjohn Company and Smith, Kline and French Foundation for support. This work was supported in part by NIH grants Ca 04739 and Ca 11198.

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