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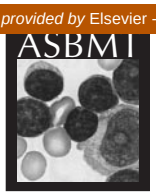

Oral Valacyclovir versus Intravenous Acyclovir in Preventing Herpes Simplex Virus Infections in Autologous Stem Cell Transplant Recipients

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ABSTRACT

Patients who are seropositive for herpes simplex virus (HSV) and are undergoing autologous marrow or peripheral blood stem cell transplantation require prophylaxis for HSV infection. Most prophylaxis regimens have used intravenous acyclovir (ACY). Oral valacyclovir (VAL), the L-valyl ester of ACY, can be used to achieve plasma concentrations equivalent to levels achieved with intravenous ACY. In this study, adults undergoing autologous stem cell transplantation were randomized to receive ACY, 250 mg/m^2 intravenously (IV) every 12 hours from day 0 to engraftment, or VAL, 1 g orally every 12 hours from day 0 to engraftment. The primary study objective was to compare cost of HSV prophylaxis between study groups. Thirty patients were randomized to receive either oral VAL (n = 14) or IV ACY (n = 16) prophylaxis. Mean pharmacy cost of HSV prophylaxis in the patient group randomized to IV ACY was $l080 versus $320 for the group randomized initially to VAL. This study demonstrates the feasibility and significant cost savings of using oral VAL for HSV prophylaxis.

KEY WORDS

Oral valacyclovir • Intravenous acyclovir • HSV prophylaxis • Pharmacy costs

INTRODUCTION

Patients undergoing autologous marrow or peripheral blood stem cell rescue after myeloablative conditioning regimens require prophylaxis for herpes simplex virus (HSV) reactivation if they are seropositive for HSV prior to stem cell transplantation [1-3]. Various schedules of prophylaxis have been published, and most of these have used intravenous (IV) acyclovir (ACY) at a dosage of 250 mg/m^2 every 8 or 12 hours [4,5]. Some regimens begin in parallel with the conditioning regimen, and others begin at the time of stem cell reinfusion. Some regimens end with engraftment of neutrophils, but others extend until day +30 or day +100 posttransplantation. The use of IV ACY contributes substantially to the cost of the autologous transplantation procedure [6].

Valacyclovir (VAL) (Valtrex) is the L-valyl ester of ACY. Because of its superior oral bioavailability (50% versus approximately 12% for oral ACY) [7], use of oral VAL can result in plasma concentrations equivalent to levels achieved with IV ACY. Use of oral VAL instead of IV ACY could potentially result in cost savings without an expected sacrifice of efficacy in HSV prophylaxis [8]. The only disadvantage to use of oral VAL would be intolerance for oral medications during periods of neutropenia and mucositis during the nadir period of the transplantation. The ready water-solubility of the VAL caplet may allow for use of liquid suspension preparations on those days when the caplets cannot be swallowed. We therefore undertook a randomized study to compare IV ACY versus VAL for HSV prophylaxis in the autologous stem cell transplantation setting. The primary objectives of the study were to compare cost of HSV prophylaxis between study groups in the autologous transplantation setting and to document the number of days patients were unable to take either the VAL caplets or the liquid suspension. Incidence of HSV infections in patients receiving oral VAL versus IV ACY prophylaxis was also documented.

Table 1. *Patient Demographics*

	Overall	VAL Arm	ACY Arm
Total	30	14	16
Sex			
Male	14	4	10
Female	16	10	6
Age, median (range), y	50.0 (26-69)	48.5 (27-69)	50.0 (26-65)
Diagnosis			
Lymphoma	13	7	6
Breast cancer	3	2	1
Acute myelogenous leukemia	4	1	3
Multiple myeloma	10	4	6
Conditioning regimen			
BCNU/VP-16/Ara-C/CY	11	4	7
BCNU/VP-16/Ara-C/melphalan	2	2	0
Busulfan/cytoxan	4	3	1
Melphalan/VP-16/carboplatin	2	1	1
Melphalan	10	4	6
Other	1	0	1
Transplant cell type			
PBSC	All patients		

PATIENTS AND METHODS

Study Design

All HSV seropositive adult patients who were undergoing autologous stem cell transplantation during the timeframe of the study were offered study participation. Those who gave informed consent in accordance with policies of the Research Subjects Review Board of the University of Rochester were randomized to 1 of 2 prophylaxis regimens in a nonblinded fashion using a computer program maintained by the Department of Biostatistics. The 2 regimens examined were: (1) ACY 250 mg/m^2 IV twice per day (BID) from day 0 (day of stem cell infusion) until the day of engraftment (absolute neutrophil count [ANC] >500/mm^3 for 3 consecutive days) or discharge, whichever occurred first and (2) VAL, 1 g BID from day 0 (day of stem cell infusion) until the day of engraftment (ANC >500/mm^3 for 3 consecutive days) or discharge. VAL could be taken either as caplets or as an oral suspension. On days when patients had mucositis or gastrointestinal status that precluded swallowing the VAL caplets, nursing staff dissolved the caplets in ≥30 mL liquid of the patient's choice. If patients were unable to ingest either preparation, IV ACY was substituted at a dosage of 250 mg/m^2 every 12 hours on those days only. Seropositive patients were excluded only if (1) measured or calculated creatinine clearance was <50 mL/min or serum creatinine was >2.0 mg/dL prior to beginning the conditioning regimen, (2) known allergic reactions to either ACY or VAL had occurred in the past, or (3) known active HSV infection was present at time of prophylaxis initiation.

Variables Monitored during the Study

Doses of both ACY and VAL for patients with renal impairment were adjusted based on published recommendations. Patients were monitored daily with complete blood counts and chemical profiles. Hepatic enzymes were checked 3 times per week. Patient mucositis was graded daily according to the Nebraska scale [9] by staff nurses assigned to the patient. A pharyngeal viral culture for HSV was performed on day 0, day +10, and day +30 or first visit after discharge.

Data Analysis

Pharmacy costs were compared for those patients randomized to the VAL versus the ACY treatment arm, and the extent to which patients were unable to ingest VAL in either caplet or liquid form was documented. It was determined that with 15 patients per treatment arm, the study would have 90% power to detect a dollar cost ratio of 2.0 between the VAL and ACY groups. Means and standard deviations were calculated, and differences between subject groups were analyzed using the Student *t* test.

RESULTS

Thirty patients were randomized to receive either VAL (n = 14) or ACY (n = 16). During the time frame of the study, 125 patients underwent autologous stem cell transplantation at the University of Rochester and were screened for this study. The opportunity to participate in the study was presented to 45 eligible patients, 15 of whom refused participation. The most common reason for patient exclusion during screening was HSV seronegativity. One patient had an unexpected positive result for an HSV culture obtained at day 0. This patient had been asymptomatic without oral lesions and was randomized to the VAL treatment arm. Results of HSV cultures at day +10 and day +30 were subsequently negative. No other patients developed documented HSV infection during treatment or follow-up to 30 days. Patient demographics are shown in Table 1. The mean age was the same for the patients in the ACY and VAL treatment groups. The majority of patients enrolled had lymphoma or myeloma, and all patients received myeloablative conditioning in the form of (1) BEAC (300 mg/m^2 1,3-bis(2-chloroethyl)-1-nitrosourea [BCNU], 800 mg/m^2 cytarabine [Ara-C], 800 mg/m^2 etoposide [VP-16], and 140 mg/kg cyclophosphamide total), (2) BEAM (140 mg/m^2 melphalan replacing the cyclophosphamide of the BEAC regimen, (3) BU/CY (16 mg/kg busulfan and 200 mg/kg cyclophosphamide), (4) melphalan (200 mg/m^2), or, for the 2 breast cancer patients, (5) MEC

Table 2. *Mucositis/Hyperalimentation*

		VAL Arm		
	Overall	Oral Only	Oral/IV	ACY Arm
Maximum mucositis grade, mean (range)	14.5 (11-20)	13.2 (11-15)	15.5 (14-17)	14.5 (12-20)
Days at maximum grade, mean (range)	2 (1-6)	1.7 (1-4)	2.5 (1-6)	2 (1-5)
No. of patients requiring hyperalimentation	3	0	1	2

Table 3. *Engraftment*

	Overall	VAL Arm		ACY Arm
		Oral Only	Oral/IV	
Days to ANC ≥500, mean (range)	11.6 (9-18)	10.8 (10-12)	11 (9-13)	12.3 (10-18)
Days to platelet count ≥20,000, mean (range)	13.9 (9-41)	12.3 (9-15)	15.9 (10-41)	13.4 (9-19)

(800 mg/m^2 carboplatin, 800 mg/m^2 VP-16, and 100 mg/m^2 melphalan total). One patient with breast carcinoma received the STAMP-I regimen (high-dose cyclophosphamide, cisplatin, and BCNU). All patients received a peripheral blood stem cell (PBSC) graft.

The mean of the maximum mucositis grade recorded for the VAL versus ACY groups did not differ, nor did the number of days for which the maximum mucositis grade was recorded (Table 2). Mucositis was scored according to the Nebraska scoring system, which has a range from 8 to 24. Those patients who were able to complete prophylaxis with oral VAL had a mean maximum mucositis grade of 13 ± 1.7, whereas those who required some doses of IV ACY in addition to oral VAL had a mean maximum score of 15.6 ± 0.98 ($P < .01$ by 2-sided t test). Only 3 patients received hyperalimentation during any portion of their transplantation. Time to either neutrophil or platelet engraftment was not significantly different between the 2 treatment arms (Table 3).

Only 6/14 (43%) of patients randomized initially to receive VAL required no ACY doses, whereas the other 8 required from 2 to 21 doses of IV ACY to complete HSV prophylaxis because of mucositis, nausea, or both (Table 4). Those patients who were able to complete prophylaxis with VAL alone received a mean of 24 doses. Patients randomized initially to ACY received a mean of 27 doses. Those initially randomized to VAL but switched to ACY because of intolerance received on average 15 doses of VAL and 12 doses of ACY (Table 4). Pharmacy costs during the study period were $2.50 per VAL dose and $40.00 per IV ACY dose. The mean cost of HSV prophylaxis for the group randomized initially to VAL was $320. Mean cost per patient was $59 ± $13.54 for patients able to complete prophylaxis with VAL alone versus $517 ± $318 for those needing to switch to ACY versus $1083 ± $198 for those randomized to ACY initially ($P < .001$ for mean VAL group costs versus mean ACY group costs) (Figure).

DISCUSSION

Mucosal HSV reactivation may occur in immunosuppressed subjects, and in some cases visceral dissemination or organ involvement can occur [10]. IV administration of ACY has been used for prophylaxis because of the low oral bioavailability of ACY (20%) and unpredictable absorption in stem cell transplantation patients with mucositis [11,12]. Both VAL and famciclovir have greater oral bioavailability than does oral ACY [13]. VAL is the L-valyl ester of ACY, and after conversion to ACY by hepatic and intestinal pathways, bioavailability of oral VAL is 3 to 5 times higher than that of oral ACY [7].

Previously, prospective, double-blinded, placebo-controlled studies have shown that ACY versus placebo was effective in preventing HSV reactivation when begun 3 days prior to bone marrow transplantation (BMT) and continued for 18 days [12]. Subsequent studies also confirmed the value of HSV prophylaxis in BMT patients [11], and resistance was found to develop only rarely during HSV prophylaxis [14].

This study demonstrates that the use of oral VAL as prophylaxis for HSV infections in the autologous stem cell transplantation setting results in significant cost-saving potential compared with the use of IV ACY. The cost savings calculated here involved pharmacy costs, but costs of preparation and administration of an IV drug are also considerations. Because the incidence of HSV reactivation during prophylaxis is low [12], this study was not powered to detect efficacy differences between the 2 prophylaxis regimens. No documented infections occurred during the period of screening, except for the patient who had an unexpectedly positive baseline culture.

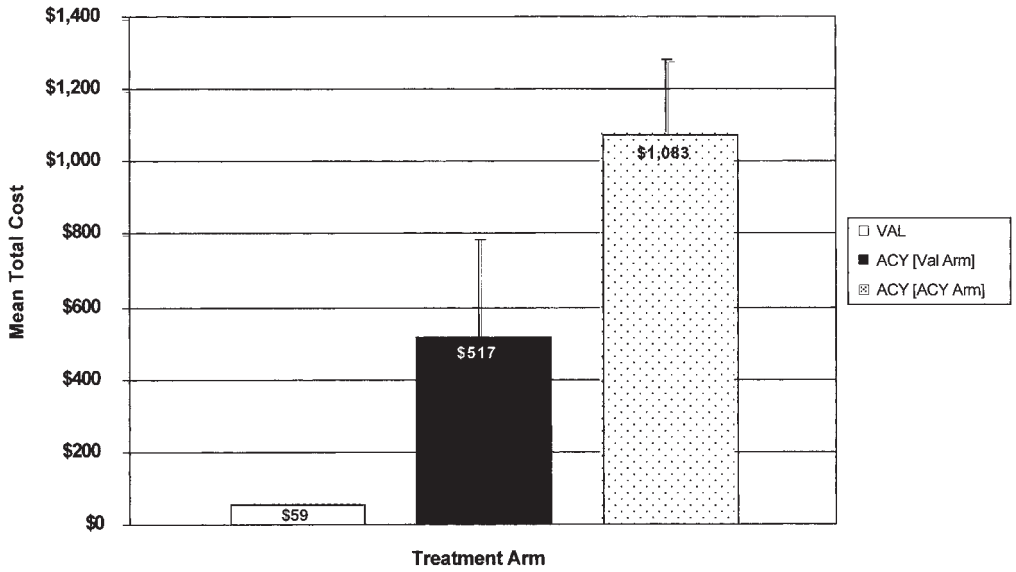
No side effects attributable to oral VAL affected transplantation course or engraftment, and at the 1-g BID dosage used here, no instances of thrombotic microangiopathy, which has been seen with higher doses of VAL (8 g/day), were noted [15]. A 500-mg BID dosage may be an effective prophylaxis dosage as well but would need to be examined in a randomized fashion. One previous study has retrospectively examined a 500-mg BID VAL dosage for HSV prophylaxis in autologous stem cell transplantation patients [16]. We chose 1 g BID as the dosage most equivalent to the 250 mg/m^2 dosage of IV ACY usually recommended for HSV prophylaxis in the stem cell transplantation setting [8].

This study also demonstrates that although the use of VAL was feasible in a population of patients undergoing myeloablative conditioning followed by autologous blood progenitor cell infusions, a significant proportion of patients receiving VAL required some doses of IV ACY to complete HSV prophylaxis because of mucositis and other gastrointestinal side effects. Nevertheless, the use of VAL, when tolerated from a gastrointestinal standpoint, resulted in significant

Table 4. *Total Cost of HSV Prophylaxis*

	Valacyclovir		
	No IV Required (n = 6)	IV Required (n = 8)	Acyclovir (n = 15)*
Valacyclovir, no. of doses			
Total	141	119	0
Mean	24	15	0
Acyclovir, no. of doses			
Total	0	93	406
Mean	0	12	27
Range		(2-21)	(22-36)
Mean cost/patient	$59	$518	$1083

*Data missing on 1 patient.



Mean total cost of HSV prophylaxis.

cost savings, and no patients developed documented HSV infections during the monitoring period of this study (up to day +30 posttransplantation), although this study was not powered to demonstrate equivalent efficacy. Further prospective studies of VAL use for HSV prophylaxis in both allogeneic and autologous stem cell transplantation patients would appear to be warranted.

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