

Blood and Marrow TRANSPLANTATION

REVIEWS

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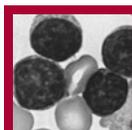
Cytomegalovirus: Is There Anything New under the Sun?

by John R. Wingard

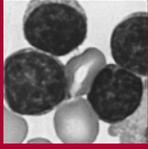
With so much success in controlling cytomegalovirus (CMV) disease, one feels almost ungrateful to furtively whisper that there is more yet to do. Still, there is the inconvenience and expense of intravenous regimens, there are toxicity issues with current regimens, and we still face late CMV disease, which is growing in frequency. Increasingly, we have also become aware that CMV-seropositive patients who undergo transplantation—even if they do not experience overt CMV disease—are at increased risk of dying in ways that are not readily apparent.

This issue of *Blood and Marrow Transplantation Reviews* originated from a transcript of a symposium that was presented at the 2005 Tandem BMT Meetings in Keystone, Colorado. The symposium addressed the question of what's new about CMV and hematopoietic cell transplantation. In the first presentation Dr. Baden describes the pharmacokinetics of valganciclovir and reviews emerging data on absorption in patients with diarrhea and gastrointestinal graft versus host disease. In the second presentation, Dr. Bachier discusses pros and cons of prophylaxis and pre-emptive therapy, the two major strategies used to control CMV infection, and he reviews recent CMV prophylaxis trials using oral regimens. In the final presentation, Dr. Boeckh reminds us of the increasing impact of late CMV disease and discusses principles of prevention and management strategies.

Clearly, challenges remain. New data, as presented in this symposium, offer possible ways to meet the challenge to improve transplantation outcomes.



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PRELIMINARY APPLICATION

**Be a part of a national organization
established to promote
education, research, and
medical development in the field of
blood and marrow transplantation.**

Full Membership is open to individuals holding an MD or PhD degree with demonstrated expertise in blood and marrow transplantation as evidenced by either the publication of two papers on hematopoietic stem cell transplantation-related research as recorded by curriculum vitae, or documentation of two years of experience in clinical transplantation as recorded by curriculum vitae or letter from the director of a transplant center attesting to the experience of the candidate.

Associate Membership is open to individuals with an MD or PhD degree who otherwise do not meet the criteria for full membership.

Affiliate Membership is available to allied non-MD or non-PhD professionals who have an interest in blood and marrow transplantation. This category is especially appropriate for nursing and administrative staff of bone marrow transplant centers, collection centers, and processing laboratories, and for professional staff of corporations that provide products and services to the field of blood and marrow transplantation.

In-Training Membership is open to fellows-in-training in bone marrow transplantation programs. A letter from the transplant center director attesting to the applicant's training status is required.

Included in the membership fee is a one-year subscription to *Biology of Blood and Marrow Transplantation*.

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2006 BMT TANDEM MEETINGS WILL BE FEB. 16-20 IN HAWAII

The combined 2006 annual meetings of ASBMT and the Center for International Blood and Marrow Transplant Research (CIBMTR) will be February 16-20 at the Hawaii Convention Center in Honolulu.

Abstracts can be submitted to the BMT Tandem Meetings on the ASBMT Web site at www.asbmt.org. The deadline is October 3.

Recent advances in the broad field of cellular therapy and blood and marrow transplantation will be addressed in plenary sessions, concurrent sessions, workshops, poster sessions and symposia. In addition to the program highlights listed below, 54 original abstracts will be selected for oral presentation.

THURSDAY, FEBRUARY 16

- Cancer Vaccines/T-Cell Therapy
Jeffrey Mouldrem, Stanley Riddell, Hyam Levitsky
- Genomics and BMT
John Shaughnessy, Bart Barlogie, James Downing, Sandeep Dave
- Biology of Aging
William Ershler, Andrew Artz, Evan Keller
- CIBMTR-EBMT Session
Recent Key Studies
- Infectious Diseases of Transplant Patients
Eric Pamer, Michael Boeckh, Cliona Rooney
- Nanotechnology
Warren Chan, Luke Lee, Carlo Montemagno
- Biology and Treatment of Myeloma/Plasma Cell Disorders
Patrizia Tosi, Barbara Gamberi, Nichola Giuliani

FRIDAY, FEBRUARY 17

- Genomic Polymorphism
Charles Mullighan, Effie Petersdorf, Peter Parham
- Stem Cell Therapies in Children and Adolescents: Can Hematopoietic Stem Cells Be Used To Treat Disorders that Do Not Involve Blood or Cancer?
Kirk Schultz, Donna Wall
- Animal Models in BMT: What Can We Learn from Them?
Thea Friedman, Xue-Zhong Yu
- Feasibility Testing of "Serious GvHD" as an Endpoint for Clinical Trials
Paul Martin, Mary Flowers

SATURDAY, FEBRUARY 18

- Cell Trafficking and Homing
Robert Sackstein, Makoto Iwata, Thalia Papayannopoulou
- Best Abstracts Session
- E. Donnall Thomas Lecture

SUNDAY, FEBRUARY 19

- Biology and Treatment of Follicular Lymphoma
Randy Gascoyne, Ginna Laport, Arnold Freedman
- Mortimer M. Bortin Lecture
- Late Effects of Therapy
Gérard Socié, Linda Burns
- Reduced-Intensity Regimen: The Dose Spectrum
Sergio Giral, Brenda Sandmaier
- Practice Variation in Transplantation: How Much Is Too Much?
Stephanie Lee, Mary Eapen

MONDAY, FEBRUARY 20

- Stem Cell Biology
Irving Weissman
- From the Biology to the Clinical Use of Cord Blood Cells
Vanderson Rocha, John Wagner, Hal Broxmeyer
- Immune Reconstitution from Stem Cells to Lymphocytes
Kenneth Weinberg, Crystal Mackall, Gay Crooks
- Statistical Analysis of Transplant Outcomes
John Klein, Mei-Jie Zhang, Brent Logan
- Advances in Biology, Diagnostics and Treatment of Hodgkin's Disease
Andreas Josting, Ralf Kuppers, Joachin Yahalom
- Advances in HLA: Practical Implications for Selecting Adult Donors and Cord Blood Units
Dennis Confer, Carolyn Hurley, John Wagner

The scientific program chair for ASBMT is Claudio Anasetti, MD, of the H. Lee Moffitt Center, Tampa, and chair for the CIBMTR is Olle Rindén, MD, PhD, of Karolinska Institute, Stockholm, Sweden.

Related Conferences

In addition to the five days of scientific sessions for BMT clinicians and investigators, there will be five related conferences and courses:

- BMT Pharmacists (*Feb. 15-16*)
- Clinical Research Professionals and Data Managers (*Feb. 15-17*)
- BMT Center Administrators (*Feb. 17-18*)
- Transplant Nursing (*Feb. 18-20*)
- BMT Center Medical Directors (*Feb. 19*)

Early Registration

The early registration deadline is October 3. Online meeting registration can be accessed at both the ASBMT Web site, www.asbmt.org, and the CIBMTR Web site, www.cibmtr.org.

Housing

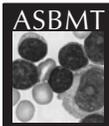
The housing deadline is January 3, 2006, after which accommodations are on a space-available basis. The headquarters hotel is the Ala Moana Hotel, located across the street from the convention center and about three blocks from Waikiki Beach. The reserved housing block also includes hotels on the beach.

Online housing reservations can be accessed at the ASBMT and CIBMTR Web sites, where information about the Tandem BMT Meetings is continuously updated.

40 TRAVEL GRANTS AVAILABLE FOR BMT TANDEM MEETINGS

The ASBMT Executive Committee has announced 40 travel grants of \$1,000 each for young investigators (not more than five years in the BMT field) submitting abstracts to the 2006 Tandem BMT Meetings next February in Honolulu, Hawaii.

The grants will be awarded to authors of the submitted abstracts earning the highest scores by the Abstract Review Committees.



What's New in Cytomegalovirus and Hematopoietic Cell Transplantation?

Adapted from a CME symposium presented at the American Society for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research 2005 Tandem BMT Meetings, February 13, 2005, Keystone, Colorado. This program is supported by an unrestricted educational grant from Roche Pharmaceuticals.



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Faculty Disclosure

As an accredited CME provider, the Medical College of Wisconsin must ensure balance, independence, objectivity, and scientific rigor in all its individual or jointly sponsored educational activities. The authors who contributed to this publication have disclosed the following relationships:

Carlos R. Bachier, MD, has indicated that he has received research support from Roche Laboratories Inc.

Lindsey R. Baden, MD, has indicated that he has received research support from Roche Laboratories Inc.

Michael Boeckh, MD, has indicated that he is a consultant for Bayer Healthcare, Roche Laboratories Inc., Vical Inc., and ViroPharma Inc.

Valcyte® is not indicated for use in hematopoietic stem cell transplantation.

Continuing Medical Education Credit

The Medical College of Wisconsin is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Medical College of Wisconsin designates this educational activity for a maximum of 1.0 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the educational activity.

Target Audience

This program will be of value to physicians, data managers, nurses, and pharmacists who are involved in the care of recipients of blood and marrow transplants.

Educational Objectives

After completion of this activity, participants should be able to:

- Summarize the pharmacokinetics of valganciclovir in hematopoietic stem cell transplantation patients (HSCT) with graft-versus-host disease (GVHD).
- Describe methods for preventing early cytomegalovirus (CMV) infection in HSCT recipients.
- Discuss risk factors and available resources for preventing late-onset CMV infection in HSCT.

Evaluation

A course evaluation questionnaire will provide each participant with the opportunity to review this publication, to identify future educational needs, and to comment on any perceived commercial or promotional bias.

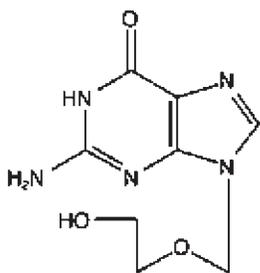
Overview

Cytomegalovirus (CMV) is a significant cause of increased morbidity and mortality in patients who undergo hematopoietic stem cell transplantation. Although progress has been made toward minimizing the impact of CMV infection and disease in this setting, it is important to review periodically the achievements made to date, identify remaining challenges, and determine possible means of meeting those challenges to provide optimal patient care and maximize positive outcomes. This program has been developed to provide state-of-the-art knowledge for use in these efforts. The management of patients experiencing graft-versus-host disease poses significant challenges, some of which can now be overcome with newly available therapies. In addition, new data are emerging on the use of valganciclovir in the prevention of both early and late CMV disease.

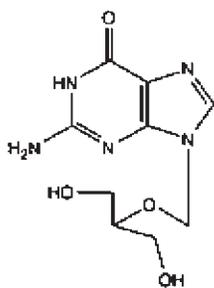
Pharmacokinetics of Valganciclovir in HSCT Patients with Gastrointestinal GVHD

Lindsey R. Baden, MD

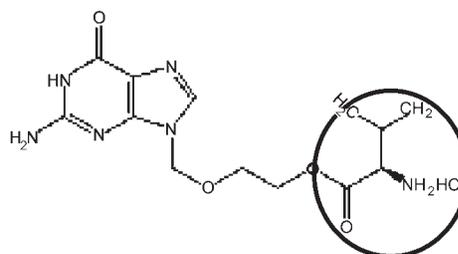
Acyclovir and ganciclovir (GCV) have been a mainstay of antiviral therapy for many years, but these medications have poor bioavailability. The addition of a valine ester substantially increases the bioavailability of both drugs from approximately 6% to approximately 60% (Figure 1). The resulting prodrugs valacyclovir and valganciclovir (VGCV) are absorbed rapidly in the intestine and are rapidly metabolized from the prodrug to the active compound through intestinal as well as hepatic pathways. The active compound undergoes very little hepatic metabolism and is predominantly renally excreted.



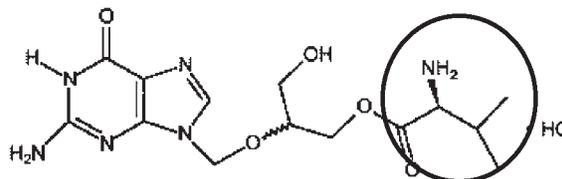
Acyclovir



Ganciclovir



Valacyclovir



Valganciclovir

Pharmacologic Considerations

Important pharmacokinetic parameters to be considered in analyzing drug bioavailability are absorption, distribution, metabolism, and elimination/clearance. On graphic representations of data, these parameters are related to the area under the curve (AUC) from 0 to 24 hours, which indicates how much drug is available during this specific time period. This value is often extrapolated beyond 24 hours based on the concentration. Another important data point is the maximum observed concentration (C-max), which is the time required for the maximum concentration to be reached.

Figure 2 illustrates the pharmacokinetics of intravenously (IV) administered GCV and oral VGCV in the intestine of a single patient who underwent a small intestine transplantation. These recently published data [1] are from a study in which investigators compared the bioavailability, determined by measuring

drug levels over 24 hours, of a single 900-mg dose of oral VGCV to that of a single 5-mg/kg dose of IV GCV. For IV GCV the C-max, which occurred approximately 1 hour after administration, was approximately 14 $\mu\text{g/mL}$, and the AUC was approximately 35 $\mu\text{g/mL}$ per hour. For oral VGCV, the C-max occurred approximately 6 hours later, with a diminished peak of the C-max of about 10 $\mu\text{g/mL}$, and the AUC was 85 $\mu\text{g/mL}$ per hour, a value that differs from other pharmacokinetic studies. A possible explanation for the results in this single case is that there was some difficulty in absorbing the oral medication because the patient had intestinal disease.

In another recent study investigating the bioavailability of GCV in its different formulations in other transplantation patients, Pescovitz et al [2] compared pharmacokinetic parameters of oral and IV GCV and VGCV administered within 1 to 6 months of transplantation in 28 liver transplantation patients.

Figure 1. Addition of a valine ester substantially increases the bioavailability of acyclovir and ganciclovir. The resulting prodrugs valganciclovir and valacyclovir are absorbed rapidly in the intestine and rapidly metabolized from the prodrug to the active compound.

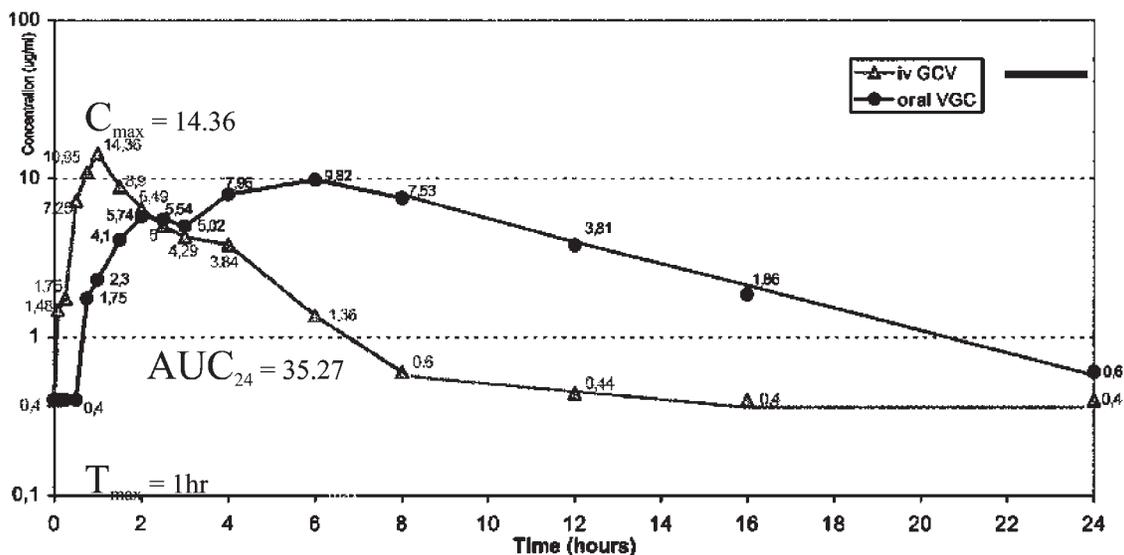


Figure 2. Pharmacokinetics of valganciclovir (VGCV) and ganciclovir (GCV) in a single patient who underwent small intestine transplantation, showing concentrations of GCV over the 24-hour dosing interval after administration of a single dose of IV GCV (5 mg/kg) and oral VGCV (900 mg). AUC_{24} indicates area under the curve through 24 hours; C_{max} , maximum observed concentration; T_{max} , time to maximum observed concentration. Reprinted with permission from [1].

In a crossover study, all patients received 3 doses of oral GCV, 1 g every 6 hours, and single doses of IV GCV, 5 mg/kg; VGCV, 450 mg; and VGCV, 900 mg. An important feature of this study was that patients with uncontrolled diarrhea, which would affect intestinal absorption, were excluded. The data showed that IV GCV serum concentrations peaked rapidly 1 hour after administration, with a C_{max} of approximately 12 or 13 $\mu\text{g/mL}$. For the 900-mg dose of VGCV, the C_{max} was delayed a couple of hours, and the peak was diminished. For the 450-mg dose of VGCV the C_{max} was approximately 3 $\mu\text{g/mL}$. AUCs were roughly equivalent for the IV GCV and the 900-mg VGCV, as were the AUCs for the 450 mg VGCV and the 3 g oral GCV, indicating that systemic exposure to GCV from oral VGCV was equivalent to that from standard oral GCV (at 450 mg) or IV GCV (at 900 mg of VGCV). Negligible amounts of serum VGCV were detected, a finding that further confirms the rapid degradation or metabolism of the prodrug, with cleavage of the valine and release of the active compound, GCV, occurring very quickly after administration.

The question of whether such findings correlate with benefit was addressed in a recent study by Paya et al [3], which looked at the efficacy of VGCV. In this report of 364 high-risk cytomegalovirus (CMV)-seronegative solid organ transplant recipients of

organs from seropositive donors, the patients received VGCV 900 mg once daily or oral GCV 1000 mg 3 times a day beginning within 10 days of transplantation and continuing through 100 days. VGCV was associated with less CMV viremia, with viremia occurrence rates of 2% in the VGCV-treated patients and 10% in oral GCV-treated patients during treatment. There was a higher incidence of neutropenia of 8.2% with VGCV compared to 3.2% with GCV; otherwise the safety profile was similar for both drugs. Overall, once-daily oral VGCV was as clinically effective and well tolerated as oral GCV for CMV prevention in high-risk solid organ transplant recipients.

VGCV in Patients with Gastrointestinal GVHD

Patients with gastrointestinal graft-versus-host disease (GVHD) may suffer oral ulcerations, mucosal injury, and diarrhea and therefore may not be able to absorb oral compounds, so caution is needed when transitioning from IV therapy to oral therapy.

In patients with gastrointestinal GVHD, some have proposed that VGCV might be useful for treating CMV [4], but others [5] have cautioned against its use because VGCV absorption has not been demonstrated in these patients. Therefore many experts recommend that until ongoing pharmacokinetics

and efficacy studies better define the role of VGCV in recipients of stem cell transplants who have gastrointestinal GVHD, induction treatment with IV GCV should be considered for patients on high levels of immunosuppressants or patients with gastrointestinal GVHD who develop CMV reactivation or infection.

Data are now available from a recently completed study of patients who had undergone allogeneic hematopoietic stem cell transplantation and who had biopsy-proven GVHD of the gastrointestinal tract with nausea and/or diarrhea or proven GVHD of the skin or liver plus diarrhea with no alternative explanation [6]. Study patients were without active CMV disease and had a neutrophil count ≥ 1000 cells/ μL . In addition, patients had adequate renal function, indicated by creatinine clearance > 60 mL/min, which is a very important consideration in managing patients treated with GCV of any form. Patients were able to consume a standardized breakfast, so they did not have uncontrolled gastrointestinal symptoms. A single dose of IV GCV (5 mg/kg) was given or a single oral dose of VGCV (900 mg) in a crossover design with a 2- to 7-day washout period. A total of 24 patients enrolled in the study, and 22 received both treatments. Patient demographic data are listed in the Table.

Figure 3 illustrates important aspects of the data on a linear scale. IV GCV concentra-

Valganciclovir Treatment of Patients with Gastrointestinal GVHD: Patient Demographics [6]

No. of patients	22
Age, mean (range), y	45 (23-63)
Sex, m/f	16/6
Underlying disease	
Lymphoma	7
Acute leukemia	5
Chronic lymphocytic leukemia	3
Chronic myelogenous leukemia	2
Multiple myeloma	2
Aplastic anemia	2
Myelodysplastic syndrome	1
GVHD	
Chronic	14
Acute (grade 2 or 3)	8
Biopsy-proven GVHD	
Gastrointestinal	19
Liver	2
None	1
Immunosuppressive drugs	
Tacrolimus, corticosteroids	9
Tacrolimus, corticosteroids, mycophenolate	1
Tacrolimus	2
Cyclosporine, corticosteroids	6
Cyclosporine, corticosteroids, mycophenolate	1
Sirolimus, corticosteroids	3
Time from transplantation, median (range), d	227 (61-988)
Creatinine clearance, mean (range), mL/min	92 (45-182)

tion peaked early, with a C-max of approximately 13 $\mu\text{g/mL}$ occurring at approximately 1 hour. With oral VGCV, a C-max of approximately 6 $\mu\text{g/mL}$ occurred approximately 5 hours after administration. These data are comparable with those seen in the Pescovitz et al study [1] in that the AUCs for the IV and for the oral medications were roughly equivalent, and the noninferiority of the oral form was demonstrated specifically; systemic exposure to GCV after 900 mg VGCV was comparable to that achieved with 5 mg/kg IV GCV. The mean plasma C-max of VGCV again was negligible, further establishing the rapidity of cleavage of the valine with release of the active moiety.

These results support the use of VGCV in patients with documented gastrointestinal GVHD who have received an allogeneic HCT complicated by gastrointestinal GvHD. However, the C-max was decreased and

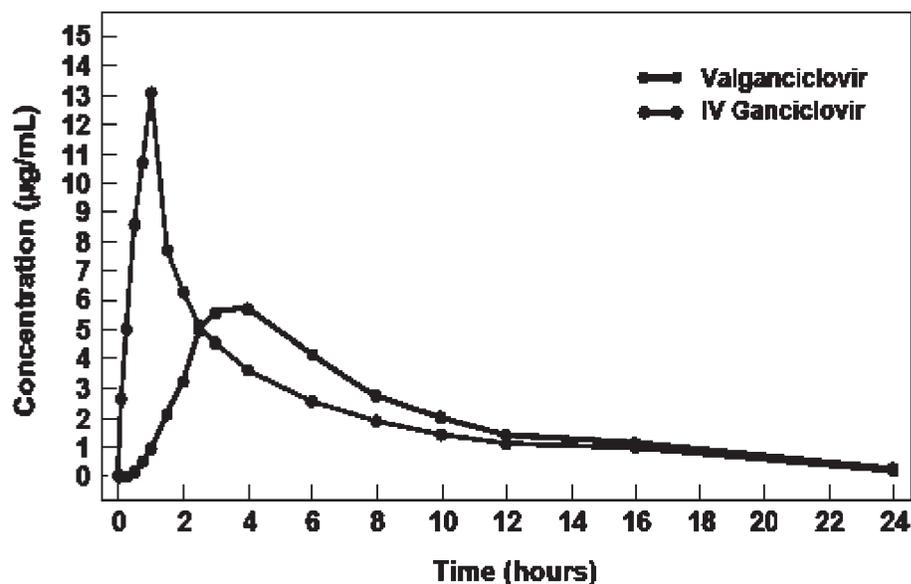


Figure 3. Mean plasma ganciclovir concentration over time for oral valganciclovir (900 mg) or intravenous ganciclovir (5 mg/kg) [6].

delayed. Given that the AUC for GCV was equivalent between the 2 formulations, these data support the role for VGCV in the management of CMV complications in this patient population.

Conclusion

In patients with documented gastrointestinal GVHD, the systemic exposure to GCV after a single dose of VGCV (900 mg) or a single dose of IV GCV (5 mg/kg) is comparable. However, the C-max is decreased and delayed in those who receive VGCV. Data support the use of VGCV in patients who have received an allogeneic transplant; however, clinical efficacy data are needed to define at what phase of treatment (prophylactic, preemptive, and/or therapeutic) VGCV should be used.

References

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6. Winston DJ, Ratanatharathorn V, Baden L, et al. Pharmacokinetics of ganciclovir following oral valganciclovir versus intravenous ganciclovir in allogeneic hematopoietic stem-cell transplant patients with stable graft-versus-host disease of the gastrointestinal tract. American Society of Hematology 46th annual meeting, San Diego, Calif. December 2004. Abstract 2223.

Prevention of Early CMV Infection in HSCT

Carlos R. Bachier, MD

There are two strategies for the prevention of early cytomegalovirus (CMV) infection and disease in CMV-seropositive patients and seronegative recipients who receive a seropositive graft. Preemptive therapy is a strategy in which patients undergo monitoring for CMV infection, and treatment is given only to those patients who develop CMV viremia. In prophylaxis, all patients receive treatment at particular intervals after transplantation with the intention of preventing CMV disease.

Preemptive therapy has been adopted as the standard for CMV prevention at most transplantation institutions because improvements in detection techniques including DNA-based methods such as polymerase chain reaction (PCR), have allowed prompt preemptive treatment and, as a result, a relatively low incidence of breakthrough CMV disease, and because patients are spared the toxic effects associated with the use of ganciclovir as prophylaxis.

Prophylactic strategies require patient monitoring, are associated with myelosuppression and increased risk of infections, and require frequent visits to clinics or arrangements for outpatient intravenous (IV) administration of antiviral medication (Table 1).

Prophylaxis Reconsidered

Despite the disadvantages, early prophylaxis for control of CMV is being reconsidered as a viable treatment option for the following reasons:

- The incidence of early CMV infection can be as high as 50% to 80% in high-risk patients, including patients who undergo highly

immunosuppressive regimens, who receive transplants from unrelated and/or mismatched donors, or who develop graft-versus-host disease (GVHD).

- In those patients who develop an initial infection, the incidence of recurrent infections after treatment is 30% to 40%.
- Patients receiving preemptive therapy have a reported 5% CMV disease breakthrough incidence.
- Patients who develop CMV infection require full therapeutic doses of ganciclovir and are thus at risk for myelosuppression associated with this therapy. This risk can be avoided by prophylactic treatment that prevents infection at lower doses.
- Infected patients are at risk for CMV syndrome, with the development of fever, malaise, and decreased white blood cell and platelet counts just prior to or concomitant with the development of CMV viremia.
- Anti-CMV oral formulations with good bioavailability have been developed that can be used for CMV prophylaxis.

Recent studies have shown that despite a relatively high success rate with preemptive strategies, CMV-seropositive patients have higher mortality rates than CMV seronegative patients [1-5]. The reasons for this poor outcome are not clear but could be related to direct toxic effects of CMV in the setting of breakthrough, late, and resistant disease; indirect effects of GVHD, particularly in patients who have been treated with T-cell depletion [2], and superimposed infections and drug toxicities associated with ganciclovir and foscarnet (Figure). Clinical trials are needed to determine if CMV prophylactic strategies can overcome this negative effect of CMV seropositivity.

Early Prophylaxis of CMV after HSCT in High-Risk Patients

In a recent multicenter randomized trial, Winston and colleagues [6] compared oral valacyclovir to IV ganciclovir for CMV prophylaxis in CMV-seropositive patients who had received an allogeneic bone marrow transplant. In addition to evaluating the new drug, this trial also provided updated information on the efficacy and safety of ganciclovir in these patients. There were no differences in the incidence of CMV infection or CMV disease, and there was a statistically significant reduction in neutropenia in patients receiving valacyclovir. Drawbacks to the use of valacyclovir are that it requires the intake of 8 g of drug per day. In another large European study, valacyclovir was more effective than acyclovir in preventing CMV reactivation in bone marrow transplantation recipients and showed a similar safety profile, but there was no difference in the frequency of CMV disease and no improvement in survival [7].

We are conducting a single-arm, multi-institutional trial evaluating valganciclovir for early prophylaxis of CMV. Participating centers are the Texas Transplant Institute and University of Texas Health Science Center in San Antonio and Baylor College of Medicine in Houston. The objective of the trial is to determine the activity and safety of valganciclovir as prophylaxis after both matched-related and -unrelated transplantation.

The study includes patients with CMV seropositivity or recipients of CMV seropositive graft from matched-related or unrelated 5/6 or 6/6 donors. Other criteria were weight >35 kg and no CMV infection at study entry. Other patient characteristics are listed in Table 2.

Table 1. Ganciclovir for Prevention of Cytomegalovirus: Prophylaxis versus Preemptive Therapy

• Preemptive Therapy
Improvements in detection techniques
Low incidence of cytomegalovirus disease
Avoids toxicities of ganciclovir
• Prophylaxis
Need for monitoring
Ganciclovir toxicity
Clinic visits for intravenous administration

Direct CMV Disease <ul style="list-style-type: none"> • Breakthrough • Late • Resistant 	Indirect GVHD (especially with T-cell depletion) Other Infections: <ul style="list-style-type: none"> • Bacterial • Fungal • Other viral 	Effects of Drug Toxicity Ganciclovir: <ul style="list-style-type: none"> • Bacterial Infections • Fungal Infections Foscarnet: <ul style="list-style-type: none"> • Other viral
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Possible reasons for higher mortality rates in cytomegalovirus seropositive than cytomegalovirus seronegative patients.

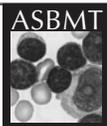


Table 2. Valganciclovir for Early Prophylaxis of Cytomegalovirus (CMV): Patient Characteristics (n = 30)

Age, median (range), y	48 (16-70)
Matched-unrelated donor transplants	12
Matched related donor transplants	18
Peripheral blood stem cell transplantation	6
Bone marrow transplantation	4
Patients with graft-versus-host disease requiring steroids	10
Patients CMV seropositive prior to transplantation	30

Patients receive valganciclovir at 900 mg daily Monday through Friday. Treatment was given beginning after engraftment on days 21 and 35 until day 100. Dosage was adjusted according to renal function and for patients who developed myelosuppression. Dose adjustments included 1 for neutropenia, 4 for thrombocytopenia, and 4 for declines in creatinine clearance.

Patient CMV status is monitored with weekly plasma polymerase chain reaction performed at a central lab. Thus far in the study, incidence of CMV infection and disease has been relatively low; 3 of 30 patients have developed CMV infection and none have developed CMV disease. In the 3 patients with CMV infection it developed relatively early, and all 3 of these patients were receiving

steroid treatment for GVHD and therefore were at high risk.

Conclusions

DNA-based techniques allow for earlier detection of CMV, and new study data have helped to identify risk factors for patients with a higher incidence of CMV infection and those at increased risk of CMV disease

Preemptive treatments are effective and are standard treatment for low-risk patients. Valganciclovir has been demonstrated to be well tolerated early after transplantation and is associated with a relatively lower incidence of CMV infection. Valganciclovir prophylaxis may be considered for hematopoietic stem cell transplantation patients who are at high risk of infection and disease, but randomized trials are needed to determine the role of these and other prophylactic strategies in these high-risk patients.

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Prevention of Late Cytomegalovirus Infection in HSCT

Michael Boeckh, MD

Late cytomegalovirus (CMV) complications, those occurring 3 months or more after transplantation, are now recognized as a cause of morbidity after allogeneic hematopoietic stem cell transplantation (HSCT). These complications usually occur in a setting of continued immunosuppression, such as in the context of chronic graft-versus-host disease (GVHD). Clinical manifestations of late CMV disease differ slightly from those seen early after transplantation. During the first 100 days after HSCT almost all patients with CMV disease have either CMV pneumonia or gastrointestinal disease or a combination of the two. Late after transplantation, more unusual manifestations of CMV tend to occur, such as CMV retinitis, CMV-associated marrow failure, or CMV encephalitis.

Impact of Late CMV Disease

Late CMV disease can cause both morbidity and mortality. It is believed to be one of the reasons why CMV-seropositive recipients of HLA-mismatched or unrelated donor transplants continue to have a poorer overall outcome after transplantation [1]. The fatality rate of late CMV disease is similar to that seen early after transplantation. Incidence figures for late CMV disease reported from different centers range from 3% to 17%. On examination of the risk factors for late CMV disease, the reasons for these differences in incidence rates become apparent.

Risk Factors for Late CMV Infection

Late CMV disease occurs in a setting of continued CMV-specific T-cell immunodeficiency. Surrogate markers for this immunosuppression are active GVHD, high doses of steroids (> 1 mg/kg of prednisone), low CD4 counts, and treatment with donor lymphocyte infusions. These conditions in combination with early CMV reactivation or extended use

of anti-CMV treatment or prophylaxis increase the risk for late CMV complications.

Outcome of Late CMV Infection and Disease

Not only CMV disease but also asymptomatic CMV viremia is associated with late mortality in patients who are seropositive allograft recipients. We conducted a study of 146 CMV-seropositive allograft recipients who were alive and without relapse of the underlying disease at day 80 after transplantation [2]. CMV-seropositive patients were studied prospectively for CMV infection (quantitative pp65 antigenemia, quantitative CMV-DNA, blood culture), T-cell immunity (CMV-specific CD4⁺ T-helper and CD8⁺ cytotoxic T-lymphocyte responses, CD4 and CD8 T-cell count, absolute lymphocyte count), and other transplantation-related factors. Both polymerase chain reaction (PCR)-confirmed CMV infections and CMV antigenemia were associated with an increased mortality in extensive multivari-

able models that controlled for other factors that are usually associated with mortality. For example, a positive plasma PCR result had an adjusted relative risk for late mortality of 13.1, and higher levels had even higher relative risks.

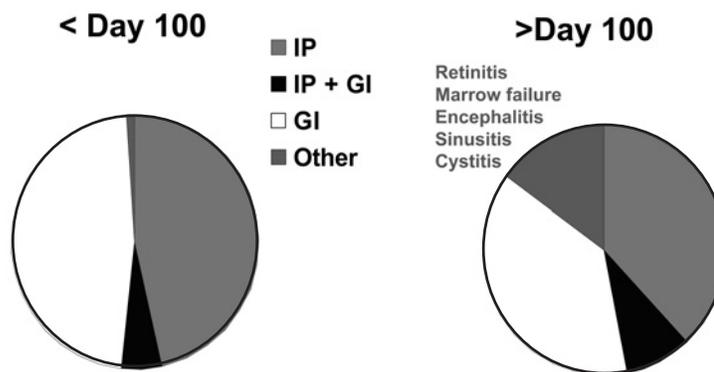
Prevention Strategies for Late CMV Disease

Strategies to prevent late CMV infection are similar to those used for prevention of early CMV disease. One strategy is prophylaxis, which covers both direct lytic effects of CMV, such as pneumonia or gastrointestinal disease, and indirect effects, which include an increased risk of bacterial and fungal infections and, in some specific settings, a higher risk of GVHD. Preemptive therapy is a more targeted approach based on virologic monitoring.

Based on current data, patients who are at risk for late CMV complications and should have continued surveillance are CMV-seropositive and CMV-negative recipients of CMV-positive allografts who had a CMV infection during the first 100 days posttransplantation or who received ganciclovir prophylaxis plus continued immunosuppression. Surrogate markers for continued immunosuppression are GVHD requiring systemic treatment, use of high-dose steroids, T-cell depletion, or treatment with donor leukocyte infusion.

The treatment strategy used at the Fred Hutchinson Cancer Research Center is summarized in Table 1. Patients with a positive plasma PCR at a level of 1000 copies/mL receive treatment with ganciclovir or valganciclovir administered according to a regimen that is very similar to what is done during the first 3 months after transplantation (ie, induction dosing for 1 week or until viral load declines, whichever is later, followed by maintenance dosing until viral load is undetectable).

An important question is how long monitoring should be continued. The monitoring period may vary from patient to patient depending on the level of immunosuppression. If assays for T-cell immunity are available, those can be used to determine when to stop monitoring. It is reasonable to discontinue monitoring if detectable CMV-specific T-cell function is observed. Another method of determination is to look at immunosuppressive drugs, such as steroids



Clinical manifestations of late cytomegalovirus (CMV) disease in hematopoietic stem cell transplantation patients. The clinical manifestations of late CMV disease are slightly different from those seen early after transplantation. Late after transplantation more unusual manifestations such as retinitis, marrow failure and encephalitis are seen. IP indicates interstitial pneumonia; GI, gastrointestinal.

and anti-T-cell agents. Whether the patient is still receiving donor leukocyte infusions is an important consideration as well. Documentation of several negative assay tests may be an indication that monitoring can be discontinued. At the Fred Hutchinson Cancer Research Center, if the patient has no or very minimal systemic immunosuppression with no or very minimal use of systemic steroids, we wait until the patient has 2 or 3 negative CMV tests before we stop monitoring. This point is reached between 3 or 12 months in most patients, or later after transplantation in some patients with severe chronic GvHD.

Table 1. Prevention of Late CMV Disease: The Fred Hutchinson Cancer Research Center Approach

Preemptive therapy: 2-3 weeks (until negative assay)

Options	Issues
Ganciclovir	IV, neutropenia
Valganciclovir	Limited randomized control trial data, neutropenia
Foscarnet	IV, toxicity (renal, electrolytes)
Cidofovir	IV, No randomized control trial, toxicity (renal, neutropenia)

Duration of monitoring: until 6-12 months after HCT

Indications that monitoring can be discontinued:

- Detectable CMV-specific T-cell function
- No or minimal systemic immunosuppression
- No or minimal systemic steroids
- No anti-T-cell agents
- No donor leukocyte infusion
- Several negative surveillance assays

Treatment of Late CMV Disease

Preemptive treatment

For pharmacotherapy of late CMV infection, a drug such as valganciclovir that can be given orally would be preferable because many patients no longer have an intravenous (IV) line. There are no randomized trials, however, addressing specifically the use of valganciclovir for preemptive therapy in the late period after transplantation. Studies have shown that valganciclovir is well absorbed and has an area under the curve similar to IV ganciclovir [3], and this seems to be true even in cases of mild to moderate gastrointestinal GVHD [4]. However, it should be pointed out that valganciclovir must be taken with a meal, so the patients must be well enough for oral food intake.

Relatively limited data are available to indicate whether valganciclovir can be used exclusively for treatment of CMV infection or disease in hematopoietic stem cell transplant recipients. The issue here is whether the AUC is the most important pharmacokinetic parameter or if the peak levels generated by IV ganciclovir are more important. There is no study addressing this issue directly. Studies that support the exclusive use of valganciclovir for treatment include the first comparative trial of CMV retinitis, which showed noninferiority of valganciclovir to IV ganciclovir [5]. Another small randomized pharmacokinetic trial presented last year at the European Group for Blood and Marrow Transplantation meeting suggested that valganciclovir induction

treatment reduces viral load in proportions similar to those obtained with IV ganciclovir [6]. Preliminary results from an ongoing uncontrolled cohort study [7] suggest that preemptive therapy with valganciclovir is effective. Finally, we have found in an ongoing randomized prospective trial that use of valganciclovir in the maintenance phase of preemptive therapy seems to be working well. We have treated 25 plus patients and have achieved control of viral load in all of these patients.

Prophylactic Treatment

Prophylaxis is the other potentially attractive option for treatment of late CMV disease. A scientific rationale for prophylaxis is that it covers indirect effects of CMV and prevents not only CMV disease but also viremia, which is also associated with a mortality risk. Several options exist for late prophylaxis. These include pharmacologic and immunologic interventions. Each of the pharmacologic choices has characteristics that cause some difficulty. Valacyclovir is only moderately effective and requires a high pill burden. A concern with valganciclovir is hematologic toxicity. Cidofovir has an attractive dosing schedule but requires IV administration, and it also has renal, hematologic, and potentially ocular toxicity. T-cell therapy is available at some centers, but there are still some obstacles to widespread use, including the requirement for a CMV-seropositive donor and an interaction with steroids, which inactivate T-cells at doses of 1 mg/kg of prednisone and higher.

There are several new strategies in various stages of development, including both drugs and vaccination strategies that are in various stages of evaluation at this point (Table 2).

Table 2. Prevention of Late Cytomegalovirus Infection and Disease: New Strategies

Strategy	Status
• Drugs	
Maribavir (UL 97)	Phase I/II in HSCT
Nonnucleoside inhibitors (DNA maturation)	Preclinical
Cidofovir lipid conjugates	Preclinical
• Vaccination	
Donor +/- recipient	Phase I/II in HSCT donor planned

The treatment closest to clinical utility is a new drug called maribavir, an oral drug that targets the UL97 of CMV. Maribavir is presently being evaluated in a phase I/II study in SCT centers in the United States. Other compounds and strategies are in earlier stages of evaluation.

Summary

Late complications of CMV can occur in high-risk patients. Patients at risk are seropositive or donor-positive/recipient-negative patients who had a CMV infection during the first 3 months or who received ganciclovir or valganciclovir or foscarnet prophylaxis and also have continued severe immunosuppression indicated by low CD4 counts, active GVHD requiring systemic treatment, use of high dose steroids for any reason, use of donor leukocyte infusion, or have undetectable CMV-specific T-cell responses. Asymptomatic infection is predictive for late CMV disease and late mortality. Therefore, prolonged monitoring and preemptive therapy is recommended and should be continued until immunosuppression is improved and several negative tests are documented. Prophylactic treatments for late CMV disease are being evaluated in randomized trials.

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Questions and Answers

Participant: What advice would you give to community physicians as to methods of CMV detection?

Dr. Baden: An important consideration is whether samples must be shipped to an outside laboratory, or if the test can be performed within your city, town, or community. Antigenemia testing should not be used if you have to ship the samples because quantitation is unreliable and sensitivity suffers, so if you have to use an outside lab, we recommend DNA-based detection methods. The most commonly used is quantitative PCR.

Participant: Does the high fatality rate of late CMV infection that you quoted reflect data that predate the assays that we now have to pick up CMV infection very early on?

Dr. Boeckh: Yes, these data are from the mid 1990s and are only for CMV pneumonia. Gastrointestinal disease has very limited mortality. Patients who develop CMV pneumonia in the setting of high immunosuppression may still do very poorly, however. By definition, once the pneumonia has developed the diagnostic method, even if a very effective one was available, has failed.

Participant: Do you have any pharmacokinetic data for children? Any advice regarding pediatric dosage?

Dr. Baden: No. I would like us to have such data.

Participant: How do you define drug resistance?

Dr. Boeckh: I would define it as an atypical mutation in the gene that has been associated with ganciclovir. **Dr. Bachier:** Whatever detection method you are using, I would then look for which determinants have led to the resistance since it does affect the choice of alternative therapies.

Participant: What recommendations do you have for a patient who continues to have viremia or has relapses? Is this drug resistance?

Dr. Bachier: CMV is a chronic viral infection so we do not eradicate it and we do not sterilize. Host immunity is going to determine reactivation or relapse, and I think we have to be careful about the terminology we use for CMV infection and relapse. CMV is there; if the host immunity fails, CMV will reactivate. That does not mean drug resistance. In managing such a case it is important to know what is going on with the antiviral therapy at the time there is evidence of increasing viral reproduction. In a patient on full-dose ganciclovir or valganciclovir, a rising viral load, even if it is the first episode of treatment, is very compelling evidence that there is some type of resistance. If the patient receives a course of therapy, completes it, and months go by and then there is a relapsing episode, even if it is their fifth, I am not sure that implicates the

antiviral strategy. The selective pressure needs to be proximate to the event of reactivation

Participant: How do you treat CMV pneumonia?

Faculty: For early CMV pneumonia, which has a high mortality, one needs to move quickly with the best therapies even without great evidence, because of the associated morbidity. We use high-dose IV Ig, every other day \times 4 doses in addition to antiviral therapy and maximal supportive care. Fortunately CMV pneumonia is a relatively rare event now. We do not see it that often.

Historically, the use of IV Ig has never been established in a prospective randomized trial. There were about 3 or 4 cohort studies in the late 1980s to early 1990s that showed improved outcome, and ever since it has been used. One interesting study in South America looked at patients who could not afford IV Ig because of their socioeconomic situation and compared their outcome with IV Ig treated patients and did not find a difference. Because you would suspect that the patients without IV Ig treatment would have had other factors against them, the fact that a difference was not found is compelling, but technically this was not a randomized trial. So there is still some uncertainty, but I personally would give it the benefit of the doubt and just give it. That probably it holds true for most of the trial centers.



Journal Watch

A scan of recent medical literature identified these articles of special importance in the science and clinical application of blood and marrow transplantation.

Kustikova O, Fehse B, Modlich U, et al: Clonal dominance of hematopoietic stem cells triggered by retroviral gene marking. *Science*. 2005;308:1171-1174.

Replication-defective retroviral vectors have long been used in genetic marking studies. Many retrovirally marked genes have been linked to experimentally induced tumors in mice; other genes might have potential effects on stem cell kinetics. This study evaluated the effects of retroviral gene “hits” on hematopoietic stem cells (HSCs).

Experiments were performed in healthy mice in which hematopoiesis was dominated by no more than a few clones after serial bone marrow transplantation. Twenty-two different insertions were mapped in 6 primary recipients of cells marked with full-length variant human CD34 (fCD34), while 19 insertions were mapped in 6 recipients of tCD34 cells. Sixteen secondary recipients were followed up for 22 weeks after receiving bone marrow cells from primary recipients, focusing on true HSCs with serial repopulation activity.

A total of 29 insertions were recovered from clones dominant in the serially transplanted recipients. All of the insertions involved loci with known or potential roles in HSC self-renewal or survival. Of 12 insertion sites studied, all showed evidence of transcriptional dysregulation.

Retrovirally marked genes can trigger long-term clonal dominance of nonmalignant HSCs in mice. The preferential survival of these long-term repopulating clones may result from transcriptional dysregulation of their insertion sites, without necessarily leading to malignant transformation. The findings in this mouse model may contribute to new approaches to diagnostic gene marking and to identification of genes affecting stem cell turnover.

Dezawa M, Ishikawa H, Itokazu Y, et al: Bone marrow cells generate muscle cells and repair muscle degeneration. *Science*. 2005; 309:314-317.

Bone marrow stromal cells (MSCs) have many potential uses in cell transplantation therapy. The use of this therapeutic approach for muscle degenerative diseases will require techniques of controlling the differentiation of MSCs into functional skeletal muscle cells. An approach to inducing high-purity skeletal muscle cells from a large population of MSCs is presented.

Skeletal muscle lineage cells were induced from established populations of general adherent rat and human MSCs. Single-cell clonal cultur-

ing studies suggested an efficiency rate of 89%, with most of the proliferation-competent cells demonstrating myogenic potential. Muscle lineage cells developed from the major population of MSCs, rather than from a subset of bone marrow-derived myogenic stem cells.

When transplanted into rats and mdx-nude mice with muscle degeneration, the induced cells differentiated into newly formed myofibers, most of which subsequently matured. Further studies documented incorporation of clonal cells into the damaged muscle, where they contributed to myofiber regeneration. Cells positive for Pax-7 contributed to myofiber regeneration after repeated muscle damage, in the absence of additional cell transplantation.

A technique of inducing skeletal muscle lineage cells from a large population of adherent MSCs is presented. This may be an efficient approach to developing large numbers of high-purity myogenic cells within a reasonable time, without relying on the rare subpopulation of myogenic stem cells. The technique uses readily available MSCs, avoids the controversy regarding embryonic stem cells, and may permit matched autologous or HLA-matched transplantation.

Wu JM, Bensen-Kennedy D, Miura Y, et al: The effects of interleukin 10 and interferon γ cytokine gene polymorphisms on survival after autologous bone marrow transplantation for patients with breast cancer. *Biol Blood Marrow Transplant*. 2005;11:455-464.

Induction of autoimmune graft-vs-host disease (GVHD) after autologous bone marrow transplantation (BMT) can be used as a form of antitumor immunotherapy. Autologous GVHD has previously been linked to increased expression of interleukin-10 (IL-10). Single nucleotide polymorphisms in the IL-10 promoter regions may influence production of IL-10 and thus interfere with the therapeutic effect of autologous GVHD. The effects of polymorphisms in the IL-10 promoter and the interferon- γ (IFN- γ) gene on the outcomes of autologous BMT were evaluated.

The study included 87 patients with metastatic, locally advanced, or high-risk multimode-positive breast cancer enrolled in three trials of autologous BMT. A Cox proportional hazards model was used to analyze the survival effects of inherited polymorphic alleles affecting cytokine gene transcription: single nucleotide polymorphisms of the IL-10 promoter regions, IL-10⁻⁵⁹² and IL-10⁻¹⁰⁸², and CA repeats in the first intron of the INF- γ gene.

Patients who had the CC allele of IL-10⁻⁵⁹²—which is associated with high production of IL-10—had significantly increased survival, hazard ratio 0.23. In contrast, patients with the weak AA IL-10⁻⁵⁹² promoter had poor survival, while those with the AC IL-10⁻⁵⁹² promoter allele had intermediate survival. This effect was independent of the clinical development of autologous GVHD. The presence of CA repeats linked to increased IFN- γ transcription was also associated with decreased survival: hazard ratio 2.34.

Gene polymorphisms affecting production of IL-10 and IFN- γ may influence overall survival after autologous BMT for metastatic breast cancer. Factors affecting production of these two cytokines may affect immune reconstitution and thus influence the clinical outcomes of patients with otherwise similar risk factors. Identification of these polymorphisms may have implications for clinical management.

Sawitzki B, Kingsley CI, Oliveira V, et al: IFN- γ production by alloantigen-reactive regulatory T cells is important for their regulatory function in vivo. *J Exp Med*. 2005;201:1925-1935.

CD4+ regulatory T cells (T reg cells) play a central role in in vivo immune responsiveness, but the involvement of cytokines in this immunoregulatory activity remains unclear. In a previous study, the authors found that pretreatment with donor alloantigen plus anti-CD4 therapy leads to the generation of donor-specific CD4+ T reg cells that suppress skin graft rejection, mediated by naive CD45RB^{high}CD4+ T cells. Further experiments were performed to evaluate cytokine expression by alloantigen-reactive T reg cells.

Mice were pretreated with donor alloantigen and anti-CD4 antibody, then rechallenged with donor alloantigen. Twenty-four hours after alloantigen challenge, expression of interferon- γ (IFN- γ) mRNA by CD25+CD4+ T cells increased by five times. In contrast, there was no significant change in IFN- γ mRNA expression by CD25-CD4+ T cells. The increase in IFN- γ expression was highly specific to the alloantigen used, and did not reflect contamination by recently activated or antigen-experienced T cells.

In further in vivo experiments, giving neutralizing anti-IFN- γ antibody and cotransferring CD45RB^{high}CD4+ T cells into *Rag*^{-/-} skin graft recipients resulted in a 100% graft failure rate. Studies in IFN- γ -deficient mice revealed a sharp drop in the generation and function of alloantigen-reactive T reg cells.



INF- γ appears to play a central role in the function of alloantigen-reactive T reg cells in developing tolerance to donor alloantigens *in vivo*. The findings may help to explain the direct effects of T reg cells on the proliferation and effector function of alloreactive T cells, as well as the actions of INF- γ in certain autoimmune and transplant models.

Castor A, Nilsson L, Åstrand-Grundsström I, et al: Distinct patterns of hematopoietic stem cell involvement in acute lymphoblastic leukemia. *Nature Med.* 2005;11:630-637.

The primary cellular target may have a major impact on the development and clinical outcome of leukemias. There are many questions about the relationship between normal hematopoietic stem cells (HSCs) and leukemic stem cells (LSCs), including how deeply the normal HSC compartment is affected by leukemia. Patterns of HSC involvement were assessed in three clinically and genetically distinct subtypes of acute lymphoblastic leukemia (ALL).

Blood and bone marrow samples were obtained from patients with various types of ALL. Patterns of HSC and lymphoid progenitor origin, LSC identity, and the final outcomes of the normal HSC compartment were assessed by means of fluorescence-activated cell sorting, clonality tracing, and *in vivo* LSC reconstitution.

Analysis of t(12;21)-carrying ALLs suggested that the *ETV6-RUNX1* (sometimes called *TEL-AML1*) fusion arose in a B-cell-committed progenitor. In these cases, the CD34+CD38-CD19- compartment remained normal in size and phenotype, without clonal involvement. Major breakpoint *BCR-ABL1* fusions encoding P210 BCR-ABL1 had their origin in multipotent HSCs, whereas minor *BCR-ABL1* fusions encoding P190 BCR-ABL1 arose from B cell-committed progenitors. Thus the two types of BCR-ABL1 ALLs were distinct from both a biologic and clinical standpoint. For all three types of ALL studied, a committed B progenitor phenotype was demonstrated.

In all patients studied, normal and leukemic repopulating stem cells could be prospectively separated from each other. In the *ETV6-RUNX1* and P190 BCR-ABL1 ALLs, the expanding LSC population did not affect the size of the normal HSC compartment.

Different types of ALL originate and transform at different stages of hematopoietic development. t(12;21)-Carrying ALLs originate from committed B-cell progenitors; patterns of HSC and committed B cell-progenitor involvement differ for P190 BCR-ABL1- vs P210 BCR-ABL1-

positive ALLs. The findings may lend new insights into the genetic targets of the leukemic transformation process and thus contribute to new diagnostic and treatment approaches.

Peggs KS, Hunter A, Chopra R, et al: Clinical evidence of a graft-versus-Hodgkin's lymphoma effect after reduced-intensity allogeneic transplantation. *Lancet.* 2005;365:1934-1941.

For Hodgkin's lymphoma patients with multiple relapses or treatment-refractory disease, there is a low chance of cure with conventional chemotherapy. Allogeneic stem cell transplantation has been tried in this group of patients. However, experience to date has shown high rates of mortality unrelated to relapse with no clear evidence of a graft-vs-tumor effect. The effects of reduced-intensity allogeneic transplantation were evaluated in patients with multiply relapsed Hodgkin's lymphoma, including evidence of a graft-vs-tumor effect.

The experience included 49 patients with multiple relapses of Hodgkin's lymphoma. The patients were 24 women and 25 men, median age 32 years. Ninety percent had disease progression despite autologous transplantation. Median time since diagnosis was 4.8 years, during which the patients had received 5 courses of treatment. All patients received reduced-intensity allogeneic transplantation, 63% from matched-related and 37% from matched-unrelated donors. To reduce the risk of graft-vs-host disease (GVHD), T-cell-depletion was performed in both the recipient and the graft. Patients were followed up for a median of 967 days after transplantation.

The engraftment rate was 100%, with a median CD34+ cell dose of $4.8 \times 10^6/\text{kg}$. Before donor lymphocyte infusion, grade II to IV acute GVHD was present in 16% of Patients and chronic GVHD in 14%. One-third of patients underwent donor lymphocyte infusion more than 3 months after transplantation for residual disease or progression—grade II to IV GVHD developed in 38% of this group and chronic GVHD in 31%.

The response rate to infusion was 56%, including 8 complete responses and 1 partial response. At a median follow-up of 730 days, non-relapse related mortality was 16.3% overall, 34.1% for patients with unrelated donors, and 7.2% for those with related donors. Actuarial 4-year overall survival was 55.7% for the entire sample, 62.0% for patients with related donors, and 45.1% for those with unrelated donors. Four-year progression-free survival was 32.4%, 36.3%, and 22.6%, respectively.

Reduced-intensity allogeneic transplantation offers a chance for durable response in patients with multiply relapsed Hodgkin's lymphoma and substantial previous treatment. The study demonstrates low non-relapse-related mortality, along with evidence of a clinically relevant graft-vs-tumor effect. The preliminary findings await confirmation in future trials.

Sanchez-Guijo FM, Sanchez-Abarca L-I, Bueno C, et al: Long-term immune recovery of patients undergoing allogeneic stem cell transplantation: a comparison with their respective sibling donors. *Biol Blood Marrow Transplant.* 2005;11:354-361.

Recovery of immune function after allogeneic stem cell transplantation has a major impact on long-term clinical outcomes. Although many studies have evaluated immune recovery during the first year after allo-SCT, few have included longer follow-up. Immune recovery 2 years after allo-SCT was compared with that of sibling donors.

The study included 38 patients who had undergone matched related donor all-SCT. In each case, time since transplantation was over 1 year—median 769 days. For both donors and recipients, immunophenotypic analysis of peripheral blood dendritic cells and lymphocytes was carried out, along with functional analysis of cytokine production by peripheral blood T cells.

All allo-SCT recipients demonstrated complete bone marrow chimerism with normal absolute dendritic cell and lymphocyte counts, but there were some significant differences between recipients and donors. Recipients showed a higher number of CD16+ dendritic cells and decreased numbers of myeloid and plasmacytoid dendritic cells. The recipients also had a higher B-cell count, inversion of the normal CD4+/CD8+ T-cell ratio, and a lower number of double-positive CD4+/CD8+ T cells. Analysis of cytokine production by stimulated T cells showed an increase in T-helper 1 cytokines, ie, interferon- γ and tumor necrosis factor- α ; with a decrease in T-helper 2 cytokine, ie, interleukin-5 and interleukin-10.

The study also compared immune parameters for patients undergoing reduced-intensity conditioning vs conventional myeloablative transplantation. No significant differences were found.

Long-term follow-up reveals some significant differences in immune parameters between allo-SCT recipients and their HLA-identical sibling donors. Further study will be needed to assess the clinical relevance and time course of the differences observed.

What's New in Cytomegalovirus and Hematopoietic Cell Transplantation?

CME Assessment Test

- Which of the following is NOT true of prodrugs such as valganciclovir for treating CMV disease?
 - These drugs have less rapid intestinal absorption than older drugs such as ganciclovir.
 - Patients suffering gastrointestinal GVHD may not be able to absorb these drugs.
 - More rapid absorption of these drugs has not been conclusively correlated with increased effectiveness.
 - Patients treated with either valganciclovir or ganciclovir must have adequate renal function.
- Which of the following is true regarding the pharmacokinetics of valganciclovir in hematopoietic transplantation patients with gastrointestinal GVHD?
 - The active compound undergoes very little hepatic metabolism and is predominantly renally excreted.
 - The addition of a valine ester substantially increases the bioavailability of the drug from approximately 6% to approximately 60%.
 - Studies have confirmed the rapid degradation or metabolism of the pro-drug, with release of the active compound, GCV, occurring very quickly after administration.
 - All of the above.
- Which of the following is true regarding preemptive therapy for CMV in hematopoietic transplantation patients?
 - Preemptive therapy is a strategy in which all patients receive treatment at particular intervals after transplantation, and treatment is given only to those patients who develop CMV viremia.
 - Preemptive therapy has been adopted as the standard for CMV prevention at most transplantation institutions.
 - An advantage of preemptive therapy is that patients are spared the toxic effects associated with ganciclovir prophylaxis.
 - All of the above.
- Which of the following is true regarding prophylactic therapy for CMV in hematopoietic transplantation patients?
 - In prophylaxis, all patients receive treatment at particular intervals after transplantation with the intention of preventing CMV disease.
 - Anti-CMV oral formulations with good bioavailability have been developed that can be used for CMV prophylaxis.
 - Despite the disadvantages, early prophylaxis for control of CMV is being reconsidered as a viable treatment option.
 - All of the above.
- Which of the following is NOT true regarding CMV-seropositive transplantation patients?
 - Patients who develop CMV infection require full therapeutic doses of ganciclovir and are thus at risk for myelosuppression associated with this therapy.
 - The incidence of early CMV infection can be as high as 50% to 80% in high-risk patients.
 - Patients who develop an initial CMV infection are unlikely to suffer recurrent infection.
 - All of the above.
- Which of the following is true regarding late versus early posttransplantation CMV disease?
 - Clinical manifestations of late CMV differ slightly from those of early CMV.
 - Fatality rates for late CMV are similar to those of early CMV.
 - The usual manifestations of early CMV disease are pneumonia and/or gastrointestinal disease, whereas late CMV disease has more unusual manifestations such as CMV retinitis, marrow failure, of encephalitis.
 - All of the above.
- Which of the following is true regarding prevention strategies for late CMV disease?
 - Strategies to prevent late CMV infection are very different from those used for prevention of early CMV disease.
 - A standard CMV monitoring period has been established for all patients regardless of immunosuppression method.
 - Documentation of several negative assay tests may be an indication that CMV monitoring can be discontinued.
 - All of the above.
- Which of the following is NOT a risk factor for late CMV infection?
 - CMV-specific T-cell immunodeficiency.
 - High CD4 counts.
 - Treatment with donor lymphocyte infusions
 - All of the above.
- Which of the following is true regarding valganciclovir treatment of late CMV disease?
 - Valganciclovir must be taken with a meal, so the patients must be well enough for oral food intake.
 - For pharmacotherapy of late CMV infection, a drug such as valganciclovir that can be given orally would be preferable because many patients no longer have an intravenous (IV) line.
 - Preliminary results from an ongoing uncontrolled cohort study suggest that preemptive therapy with valganciclovir is effective.
 - All of the above.
- Which of the following is true of new treatments for CMV disease?
 - The treatment closest to clinical utility is a new drug called maribavir, an oral drug that targets the UL97 of CMV.
 - T-cell therapy is widely used at many treatment centers.
 - Like valganciclovir, cidofovir can be administered orally.
 - All of the above.

CME Assessment Test Answer Sheet

Release Date: August 31, 2005

Last Review Date: August 31, 2005

Expiration Date: August 31, 2006

Instructions

(1) Read the articles in the publication carefully. (2) Circle the correct response to each question on the Answer Sheet. (3) Complete the evaluation Form. (4) To receive CME credit, fax the completed Answer Sheet and Evaluation Form to the office of Continuing and Professional Education (414-456-6623) or mail to the Office of Continuing Education, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. No processing fee is required.

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| 2. | A | B | C | D | 6. | A | B | C | D | 9. | A | B | C | D |
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I have read these articles on what is new in CMV and hematopoietic cell transplantation, published in *Blood and Marrow Transplantation Reviews*, and have answered the CME test questions and completed the Evaluation Form for this activity.

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