Blood and Marrow TRANSPLANTATION

REVIEWS

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IN THIS ISSUE

INTRODUCTION 1

MEMBERSHIP APPLICATION 2

ASBMT NEWS 3

CME PROGRAM: SYMPOSIUM REPORT 4

Insights Into Early Empiric or Prophylactic Antifungal Therapy in a Transplant Setting

Introduction 5
Richard Champlin, MD

Current Strategies and Future Concepts for Prophylactic Therapy 5
John Wingard, MD

Clinical Considerations for Empiric and Preemptive Therapy 8
Dimitrios P. Kontoyiannis, MD, ScD, FACP

JOURNAL WATCH 12

CME ASSESSMENT TEST 15

CME ANSWER SHEET 15

CME EVALUATION FORM 16

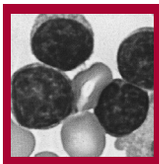
New Strategies for Fungal Infections after Hematopoietic Cell Transplantation: Prevention or Preemption?

John R. Wingard, MD, Editor

Invasive fungal infections have become the chief infectious threat to allogeneic hematopoietic cell transplant (HCT) recipients. New drugs such as the echinocandins (caspofungin, micafungin, and anidulafungin) and the extended-spectrum azoles (itraconazole, voriconazole, and posaconazole) offer more effective and safer options today. Although these potent antifungal agents make treatment prospects better, there still is considerable risk for death from *Candida*, *Aspergillus*, and other mold infections. Accordingly, considerable interest resides in figuring out what is the most effective strategy in using antifungal agents to optimize patient outcomes. Identification of risk factors allows greater focus on patients and transplantation complications that warrant a higher degree of vigilance for fungal infections. New imaging techniques and rapid diagnostic assays allow earlier institution of therapy. The success of fluconazole in dramatically reducing *Candida* infections has led to hope that similar approaches to prevent *Aspergillus* and other mold infections may also be successful.

In this issue of BMTR, the subject of how best to mitigate the threat of invasive fungal infections is addressed in the proceedings of a satellite symposium presented at the 2007 BMT Tandem Meetings in Keystone, Colorado. In the first presentation, Dr. Richard Champlin presents an overview of the problem and describes historical treatment approaches. In the second presentation, Dr. John Wingard discusses the rationale for prophylaxis and reviews the results of the various clinical trials that have tested this approach with different antifungal agents. In the third presentation, Dr. Dimitrios Kontoyiannis discusses the basis for and the data to support empiric and preemptive therapy approaches.

Enormous strides have been made in refining treatment options for invasive fungal infections. These are gradually chipping away at the threat. Yet, much work remains. Testing of which strategy optimizes patient outcomes has been started but greater understanding of what works best for whom is needed.



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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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ASBMT Position Statement Explains Role of Stem Cell Transplants in Children with Leukemia

For many children with acute myeloid leukemia (AML), transplantation of blood or marrow stem cells, combined with chemotherapy, offers improved survival compared to chemotherapy alone. Allogeneic transplantation using blood or marrow stem cells from donors related to the patient offers better survival than autologous transplants.

These are among the guidelines included in an ASBMT position statement on stem cell therapy for pediatric AML, published in the April 2007 issue of *Biology of Blood and Marrow Transplantation*.

The recommendations are based on an evidence-based review of the scientific literature on the use of hematopoietic stem cell transplantation (HSCT) in children with AML. Developed in collaboration with the National Marrow Donor Program (NMDP), the review was conducted by a panel of independent experts in transplantation and other treatments for leukemia.

For patients with certain forms of cancer, such as leukemia, and specific genetic diseases or blood disorders, HSCT can improve survival and, in many cases, cure the disease, according to the evidence-based review and the position statement. Among the specific recommendations are:

- Allogeneic HSCT after chemotherapy offers superior overall survival and leukemia-free survival when compared to chemotherapy alone for patients in first complete remission.
- Autologous HSCT or chemotherapy alone given in the first complete disease remission are equivalent in outcomes, but a lack of data on quality of life, secondary cancers and other late effects of treatment prevent a recommendation of one treatment over another.
- HSCT is recommended over chemotherapy alone in second complete remission when a suitably matched related donor is available.
- Hematopoietic stem cells donated by a matched related or unrelated donor are superior in outcome to stem cells harvested through autologous transplantation in first and second complete remission.

Posted on the ASBMT Web site at *www.asbmt.org* are the position statement on pediatric AML, the evidence-based review on pediatric AML and previously published evidence-based reviews on the use of hematopoietic stem cell transplant in treating non-Hodgkin's lymphoma, multiple myeloma and acute lymphoblastic leukemia in children and adults.

New FACT Accreditation Standards Published

Updated requirements for accreditation of hematopoietic progenitor cells transplant facilities are contained in the new Third Edition of the *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration*.

Major updates occur at three-year intervals for the standards, which are maintained by the Foundation for the Accreditation of Cellular Therapy (FACT).

Among the significant changes in the new edition are:

- Expanded quality management standards throughout
- Compatibility with FDA and European Union directives, including core Good Tissue Practices, donor eligibility, documentation requirements and biohazard warnings
- Redefined procedure volume requirements for clinical, collection and laboratory facilities
- Expanded requirements for pediatric competencies
- Incorporation of recommendation for ISBT 128 terminology and labeling

The new third edition of the Standards is available from the FACT Accreditation Office. Telephone (402) 427-8030.

FACT Market Penetration Reaches 92 Percent

More than nine out of 10 eligible blood and marrow transplant centers in the United States are either FACT-accredited or in the process of seeking accreditation.

A survey by the Foundation for the Accreditation of Cellular Therapy (FACT) found 245 centers that are eligible for accreditation. Among them, 56 percent are FACT accredited, and 36 percent are in various stages of application or inspection.

Online Presentations Address Outcomes Reporting for Allogeneic Stem Cell Transplants

A new federal law requires the measurement and reporting of outcomes of all related and unrelated allogeneic blood transplants. The transplant center-specific data will be recorded in a public registry.

Two sessions at this year's BMT Tandem Meetings addressed the details and ramifications of the new law. The presentations can be viewed online or downloaded for later viewing. The Web page is *www.asbmt.org/News/Outcomes*. There is no charge for online viewing or download.

The online programs are:

Overview of the C.W. Bill Young Cell Transplantation Program
Dennis L. Confer, MD

Requirements for the Stem Cell Therapeutic Outcomes Database
J. Douglas Rizzo, MD, MS

The Relationship between SCTOD and Other CIBMTR Programs
Mary M. Horowitz, MD, MS

ASBMT, the C.W. Bill Young Transplantation Act, and Quality Outcomes Reporting: An Update
Roy B. Jones, MD, PhD

Solid Organ Transplantation and Outcomes Reporting: An Analysis
Ian Jamieson, MBA, MHA

AGNIS: A Growable Network for Information Sharing
Dennis L. Confer, MD

CIBMTR and the Stem Cell Transplantation Outcomes Database (SCTOD)
J. Douglas Rizzo, MD, MS

How Can Centers Respond?
Patrick Stiff, MD, and Roy B. Jones, MD, PhD

Blood and Marrow TRANSPLANTATION REVIEWS

Symposium Report

Insights Into Early Empiric or Prophylactic Antifungal Therapy in a Transplant Setting

Adapted from the CME symposium "Insights Into Early Empiric or Prophylactic Antifungal Therapy in a Transplant Setting," held on February 8, 2007, at the BMT Tandem Meetings in Keystone, Colorado.
This activity is sponsored by the Medical College of Wisconsin and the Florida Society of Health-System Pharmacists and is supported by the Schering-Plough Corporation.

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Accreditation Statement

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

The Florida Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of pharmacy continuing education.

Credit Designation

The Medical College of Wisconsin designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The Florida Society of Health-System Pharmacists accredits this educational activity for 1.0 hour or 0.1 continuing education units (CEUs).

Needs Statement

The increasing incidence of fungal infections, including molds such as *Aspergillus* and Zygomycetes, is challenging the management of patients with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT). Preventive strategies are typically implemented for patients identified at highest risk for fungal infections so as to avoid the harsh consequence of these infections. Choosing between early empiric therapy and prophylactic therapy in a transplantation setting is still controversial because of such issues as spectrum of activity of current and emerging therapies, expense of therapy, and potential drug interactions. Because of the complex nature of fungal infections and risk in HSCT patients, there is a need for hematologist-oncologists to be updated on all aspects of fungal prevention—specifically, treatment-related toxicities, therapy-specific issues (eg, the spectrum of antifungal activity and patterns of selection observed), and drug-drug interactions—because new agents are emerging. Additionally, the issues surrounding current clinical trials of these new agents need to be understood so their results are not generalized to all treatment/transplant scenarios. It is important to emphasize the proper use of standard antifungal agents and the impact and potential use of newer agents under clinical investigation.

Target Audience

This activity has been designed to meet the educational needs of hematologist-oncologists, pharmacists, and other health care professionals involved in HSCT.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the spectrum of fungal infections anticipated following HSCT
- Identify risk factors for the development of fungal infections following autologous or allogeneic HSCT in patients with hematologic malignancies
- Distinguish clinical situations for the use of empiric or prophylactic antifungal therapy
- Evaluate the clinical safety and efficacy of current and novel agents designed to prevent and treat fungal infections in HSCT recipients

Faculty Disclosures

In accordance with the ACCME Standards for Commercial Support, all CME providers are required to disclose to the activity audience the relevant financial relationships of the planners, teachers, and authors involved in the development of CME content. A relevant financial relationship is one in any amount occurring in the last 12 months with a commercial interest whose products or services are discussed in the CME activity content over which the individual has control. Relationship information appears below.

Richard E. Champlin, MD, FACP has disclosed the following relevant financial relationships: consultant/advisor for Schering-Plough Corporation. Dr. Champlin will discuss the unlabeled or investigational use of a commercial product.

John R. Wingard, MD has disclosed the following relevant financial relationships: consultant/advisor for Pfizer, Merck & Co., Schering-Plough Corporation; grant/research support from Pfizer, Merck & Co.; Speakers Bureau for Pfizer, Merck & Co. Dr. Wingard will discuss the unlabeled or investigational use of a commercial product.

Dimitrios P. Kontoyannis, MD, ScD, FACP has disclosed the following relevant financial relationships: consultant/advisor for Merck & Co., Schering-Plough Corporation; grant/research support from Astellas Pharma, Enzon Pharmaceuticals, Merck & Co.; Speakers Bureau for Astellas Pharma, Enzon Pharmaceuticals, Merck & Co., Pfizer. Dr. Kontoyiannis will discuss the unlabeled or investigational use of a commercial product.

Introduction

Richard Champlin, MD

Invasive fungal infections (IFIs) are an important consideration in transplant recipients because of their compromised immune status. The urgency of early diagnosis and rapid treatment is underscored by the significant morbidity and mortality rates associated with IFIs. The most commonly encountered fungal infections are from the yeast *Candida* and *Aspergillus*. It is estimated that 5% and 15% of bone marrow transplant recipients will develop candidiasis and mold infection, respectively, in the absence of antifungal prophylaxis [1]. It is estimated that up to 20% of patients undergoing hematopoietic stem cell transplantation (HSCT) will acquire some form of IFI, with the majority of infections being aspergillosis [1]. The mortality rate associated with IFIs ranges from 40% to 100% depending on the type and number of infections in a specific patient (Table 1) [2]. A thorough understanding of the risk factors and therapeutic options (including available pharmacologic agents) is important for both the prevention and optimal treatment of IFIs in the transplantation environment.

Although most HSCT recipients do not acquire an IFI, certain factors increase the likelihood of occurrence. Increased risk for an IFI is associated with intensive myeloablative chemotherapy, development of acute and chronic graft-versus-host disease (GVHD), immunosuppressive therapy (especially corticosteroids), and the use of central venous catheters [3]. Awareness of these factors will help physicians take the necessary precautions for the prevention of IFIs. Antifungal prophylaxis, in which treatment is administered before evidence of infection is apparent, is one method for preventing IFIs. A recent survey of 526 physicians who perform HSCT revealed that over 90% administer some form of antifungal prophylaxis to their transplant recipients [4]. The azole fluconazole is the current standard for antifungal prophylaxis because of its efficacy in preventing candidiasis and reducing mortality rates compared with control in bone marrow transplant recipients [5]. More recent data have suggested that prolonged fluconazole prophylaxis (from conditioning until 75 days after transplantation) is able to significantly reduce the number of deaths due to *Candida* infection [6].

Another way of administering treatment for IFIs is through empiric therapy, which consists of treating symptomatic patients prior to obtaining definitive diagnostic results. Newer-generation azoles and echinocandins have all been used as empiric therapy. A major issue with empiric therapy is how quickly it can be administered relative to the appearance of symptoms. Early treatment of IFIs has been shown to convey a significant survival benefit [7].

A problem surrounding the treatment of IFIs is that candidiasis is becoming less prevalent, while the incidence of *Aspergillus* is increasing. This development signals a shift in attention from yeast to invasive mold infections. Treatment decisions are becoming less certain because the standard treatment using fluconazole is not effective against *Aspergillus*. A number of broad-spectrum agents have been introduced since fluconazole; their efficacy in prophylactic and empiric therapies is still being investigated. Another area of debate relates to the utility of prophylactic and empiric therapies. In this supplement, John R. Wingard, MD, discusses the factors that dictate the use of prophylactic therapy, as well as the use of narrow- and broad-spectrum antifungal agents in this setting. Dimitrios P. Kontoyiannis, MD, introduces the concept of preemptive therapy, with particular focus on available pharmacologic treatments, factors that influence IFI treatment decisions, early treatment, and methods for increasing treatment efficacy.

Table 1. Mortality Rates as a Function of Fungal Infection Type in Bone Marrow Transplant Recipients [2]

	Mortality Rates	
	Overall	Individual
Aspergillosis	84%	
Alone		75%
Other mold infections with or without *Aspergillus*		83%
Coinfection with *Candida* or cytomegalovirus		100%
Candidiasis	73%	
Alone		39%
Candidal tissue infection		90%
Mixed infection		100%

Current Strategies and Future Concepts for Prophylactic Therapy

John Wingard, MD

Epidemiologic data have indicated a 207% increase in fungal sepsis among the general population of hospitalized patients between 1979 and 2000 [8]. The increased incidence of fungal infections among the hospitalized population as a whole may suggest an increased need for antifungal protection among patients who are immunocompromised, specifically those undergoing HSCT for treatment of hematologic malignancies. In patients with hematologic malignancy, there is a greater incidence of mold infection (2.9%, represented most commonly by *Aspergillus*) than yeast infections (1.6%, represented most commonly by *Candida*), reflecting a change in prevalence of yeast versus mold infections between 1989 and 2003 [9,10]. Associated with both types of fungal infections are mortality rates that range from 40% to 100% (Table 1) [2]. Antifungal prophylaxis is one therapeutic option designed to reduce the mortality and morbidity associated with IFIs. The rationale for such an approach is to administer antifungal agents prior to infection, therefore preventing fungal colonization. Certain factors such as standard or high-risk transplantation, disease state at time of transplantation, intensity of conditioning regimen, and stem cell donor type are used to determine a transplantation patient's risk for developing a fungal infection. Successful prevention of an IFI is dependent upon using the correct treatment strategy for a specific patient and fungal type.

Treatment Options for Antifungal Prophylaxis

Prophylactic therapy in the transplantation setting is often accomplished through the use of fluconazole [5,11]. When administered as prophylaxis in bone marrow transplant recipients, 2.8% of patients receiving fluconazole had an IFI, compared with 15.8%

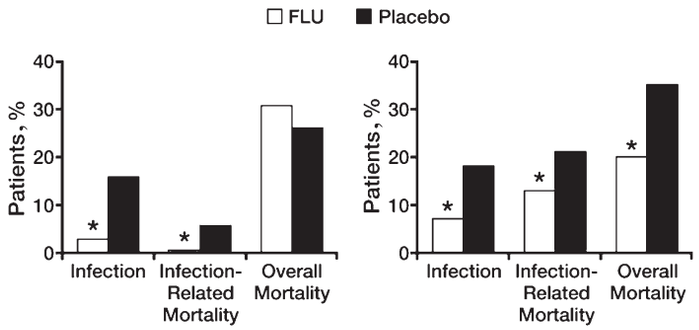

Figure 1. Effect of fluconazole prophylaxis (FLU) versus placebo on infection and mortality rates after bone marrow transplantation [5,11]. *Statistical significance between FLU and placebo.

of those receiving placebo (Figure 1) [11]. The reduced rate of infection for the fluconazole group also resulted in fewer IFI-related deaths compared with placebo (1 out of 179 versus 10 out of 177; $P < .001$), although there was no difference in overall survival (Figure 1) [11]. Adverse events associated with fluconazole were generally mild, consisting most commonly of nausea and skin rash, and occurring at a frequency similar to that seen in patients who received placebo [11]. Another randomized, double-blind study that examined fluconazole prophylaxis versus placebo (given for 75 days after bone marrow transplantation) found that far fewer bone marrow transplant recipients acquired an IFI while receiving fluconazole, as compared with patients receiving placebo (7% versus 18%; $P < .004$) [5]. The efficacy of fluconazole translated into fewer patients having to be placed on empiric amphotericin B therapy (38% versus 55% with placebo; $P < .0006$) [5]. Common adverse events for patients receiving fluconazole included nausea and seizures, neither of which differed in frequency from placebo [5]. The use of fluconazole also resulted in a reduction in the probability of death up to 110 days after transplantation ($P < .004$) [5]. Improvement in fluconazole survival rates persists even beyond completion [6]. A meta-analysis of fluconazole prophylaxis clinical trials indicated that the incidence of *Candida* infection had to be ≥15% for fluconazole to have a demonstrable benefit [12]. Thus, the benefit of candidal prophylaxis may not be significant in lower-risk situations, such as with nonablative conditioning and autologous transplantation performed for certain solid tumor cancers. The type of conditioning regimen is one of the most important determinants of the appropriateness of candidal prophylaxis. Regimens that increase mucosal injury and neutropenia also increase the likelihood of candidiasis.

Mold infections such as aspergillosis represent a larger challenge because of their increased prevalence and the lack of activity of fluconazole against mold pathogens. As a result, broad-spectrum antifungal agents have been introduced to increase efficacy while maintaining or improving upon the adverse event profile of fluconazole. Fortunately, there is a wide range of potential agents available for the treatment of aspergillosis, including polyenes, azoles, and echinocandins. The polyene class, represented by amphotericin B, has been used as a first-line treatment for antifungal treatment for decades, but has toxicity limitations because of the infusion-related reactions and nephrotoxicity associated with amphotericin B [13]. Most clinical trials examining the use of antifungal prophylaxis focus on newer-generation azole compounds and echinocandins.

Voriconazole is a broad-spectrum azole that is used off-label for antifungal prophylaxis. There are a limited number of clinical trials examining the efficacy of this compound in such a capacity. Data presented at the 2005 American Society of Hematology (ASH) meeting indicated that, in a study of 91 patients, voriconazole was statistically superior to fluconazole in preventing IFIs (2 versus 10; $P = .04$) and that the number of fatal IFIs was reduced after voriconazole prophylaxis (1 versus 5; $P < .05$) in patients receiving HSCT. Voriconazole was stopped in 2 patients for hepatic GVHD and in 1 patient for veno-occlusive disease [14]. A retrospective analysis in one center (n = 659) of 6 antifungal agents used for prophylaxis (amphotericin B lipid complex, liposomal amphotericin B, fluconazole + itraconazole, intravenous itraconazole, caspofungin, and voriconazole) indicated that voriconazole was the only agent without any mold or yeast breakthrough [15]. Voriconazole was associated with a greater frequency of toxicity than any of the other agents except for the amphotericin B formulations, the most prevalent side effects being auditory/visual hallucinations and elevated serum bilirubin [15]. Unfortunately, a number of reports have indicated that the prophylactic use of voriconazole increases the likelihood of breakthrough zygomycosis [16-19]. A more detailed investigation is needed to fully explore the suitability of voriconazole for prophylaxis.

Itraconazole is a broad-spectrum azole that has superior efficacy compared with fluconazole for the prevention of aspergillosis in patients undergoing allogeneic HSCT [20]. An open-label, randomized trial in 140 allogeneic HSCT recipients showed that itraconazole resulted in significantly fewer IFIs compared with fluconazole (9% versus 25%; $P < .01$) [20]. However, this decrease in fungal infections did not result in a significant improvement in either overall or IFI-related survival [20]. Although the adverse event profile was mild for both agents, gastrointestinal disturbances occurred more often in the itraconazole group (24% versus 9%, $P < .02$) [20]. Another open-label study of 304 allogeneic HSCT recipients indicated that itraconazole was not associated with a reduction in IFI overall, but conferred greater protection from invasive mold infections than fluconazole in patients who were able to remain on itraconazole without intolerance or removal due to toxicity [21]. Both agents were equally potent against yeast infections [21]. Like the previous study, no survival benefit was seen with itraconazole [21]. In this study, itraconazole was associated with greater gastrointestinal adverse events, hepatotoxicity, and a toxic drug interaction with cyclophosphamide, a commonly used chemotherapeutic agent. The available data support the use of prophylactic itraconazole in cases where the likelihood of invasive mold infection is very high and there remain concerns about tolerability and toxicity.

One of the newest azoles is posaconazole, which has activity against a wide range of mold species, including *Aspergillus*. When compared with fluconazole/itraconazole prophylaxis (n = 298) in neutropenic patients,

posaconazole prophylaxis (n = 304) resulted in fewer IFIs (2% versus 8%, $P < .001$) and fewer instances of invasive aspergillosis (1% versus 7%, $P < .001$) [22]. Overall survival of patients on posaconazole was 22%, compared with 16% for the fluconazole/itraconazole group ($P = .048$) [22]. In a separate study of patients who underwent HSCT and had GVHD, the total number of IFIs did not differ in patients receiving posaconazole (n = 301) or fluconazole (n = 299) prophylaxis during the 16-week fixed time period, although posaconazole prophylaxis did result in a lower number of cases of aspergillosis (2.3% versus 7.0%, $P = .006$) [23]. The number of breakthrough infections was also reduced during the drug exposure period in the posaconazole group (2.4% versus 7.6%, $P = .004$) [23]. Although overall mortalilty rates did not differ, the number of deaths due to IFIs was lower in the posaconazole group than in the fluconazole group (1% versus 4%, $P = .046$) [23]. The adverse events profile for posaconazole prophylaxis was found to be different based on the patient population. In HSCT recipients with GVHD, posaconazole and fluconazole had very similar adverse event profiles, whereas in neutropenic patients, posaconazole produced significantly more serious adverse events (ie, bilirubinemia, increased hepatic enzymes, hepatic failure, hepatitis, jaundice, diarrhea) than were seen in the fluconazole and itraconazole groups combined (6% versus 2%, $P = .01$) [22]. In both patient populations, gastrointestinal disturbances, neutropenia, liver/biliary disorders (ie, bilirubinemia, increased hepatic enzymes, increased alanine aminotransferase) were most common [22,23]. These data suggest a potential role for posaconazole prophylaxis in patients at high risk for mold infection.

The echinocandin class of agents has a novel mechanism of action against fungal species. Unlike the azoles, which target the fungal cell membrane, echinocandins (eg, micafungin) are active against the fungal cell wall. The proposed advantages of this targeting strategy are improved specificity and a reduced side-effect profile, since mammalian cells lack a cell wall. The efficacy and safety of micafungin as a prophylactic agent in patients with neutropenia undergoing HSCT has been compared with fluconazole [24]. Micafungin prophylaxis was shown to be superior to fluconazole prophylaxis in preventing IFIs (treatment success: 80% versus 73.5%, $P = .03$), whereas the occurrence of aspergillosis or candidiasis did not differ between the treatment groups [24]. There was a significantly lower use of empiric therapy for patients on micafungin prophylaxis than for those on fluconazole prophylaxis (15.1% versus 21.4%, $P = .024$) [24]. There were no significant differences between these groups in adverse event profile or overall mortality [24]. The most common adverse events for both groups were hepatic abnormalities, gastrointestinal disturbances, and injection-site reactions [24].

Considerations for the Use of Antifungal Prophylaxis

Given the options for antimold prophylaxis, should such treatment be given to all HSCT recipients in all situations? A number of factors need to be taken into account (Table 2). The type of conditioning regimen and transplant is important. Transplantations for disease states with high risk of relapse or treatment-related mortality carry a greater risk of infection, and antifungal prophylaxis should therefore be considered. HSCT procedures that use CD34-selected or T-cell–depleted stem cells increase the likelihood of aspergillosis [25]. Both nonmyeloablative and myeloablative conditioning are associated with some risk of aspergillosis, with incidence rates of 15% and 10%, respectively [25,26]. The stem cell source is important, as cord blood–derived stem cells are associated with increased times to engraftment and prolonged neutropenia, both of which increase the likelihood of aspergillosis [25]. Conversely, using targeted prophylaxis based exclusively on risk factors may exclude patients who ultimately contract aspergillosis. Intensive care unit studies have shown that fungal infections can occur even in patients who are not traditionally at risk for aspergillosis [27,28]. Recent data have also shown that patients who have risk factors that traditionally promote aspergillosis may in fact be at a lower risk for infection than originally thought [23]. It is important to be mindful that extended-spectrum azoles have specific toxicities and drug interactions (such as with liver CYP-450) that may limit their use, and also that voriconazole can promote zygomycosis [13]. Given the heterogeneity of risk for mold infections, it is difficult to know at this point whether global prophylaxis with mold-active antifungal agents is warranted. Further knowledge of the rates of IFI in different transplantation scenarios would be useful in guiding clinical decisions. However, the biggest concern is that the extended-spectrum azoles offer less improvement in clinical failure rates than does fluconazole [20].

Table 2. Considerations for Antimold Prophylaxis

Disease-related risk factors	Low- or high-risk transplantation
	T-cell–replete or depleted grafts
	Conditioning regimen
	Stem cell source
Risk stratification concerns	Prognostic factors do not identify all infected patients
	Low risk of mold infection
	Ideal start of prophylaxis; some clinical trials may contain patients with incipient infection
Drug factors	Toxicities and drug-drug interactions
	New agents have little improvement in clinical failure rate
	Some agents may encourage emergence of rare molds

The Role of Antifungal Diagnostics in Prophylactic Therapy

The diagnostic approach traditionally used to identify fungal infections consists of culture-based testing often combined with histopathology. The problem with culture-based assays is the lack of both specificity and timeliness of results, whereas histopathology often requires invasive procedures to obtain a specimen [29]. The advent of nonculture-based rapid diagnostics may allow for more accurate and timely identification of patients being considered for prophylaxis, including those with incipient infection. The enzyme-linked immunosorbent assay–based galactomannan (GM) assay is currently being used in clinical trials to detect invasive aspergillosis in patients at risk for infection. GM is a fungal cell wall polysaccharide that can be released into the blood and detected using monoclonal antibodies [29]. GM varies by species, although only *Aspergillus*-specific testing has been used clinically [29]. Recently, Ullmann et al compared the efficacy of prophylaxis with posaconazole to fluconazole in HSCT recipients with GVHD [23]. A post hoc analysis of GM assay data from this study indicated that a positive GM test at baseline was indicative of a greater subsequent occurrence of IFI than was a negative GM test [23]. While those being treated with posaconazole had a lower incidence of aspergillosis, the predictive value of a positive GM test in this study suggests that at least part of the benefit may have actually been early treatment of patients with incipient infection (ie, empiric therapy). Preemptive therapy

refers to the use of rapid diagnostics (such as the GM assay) in combination with radiology to show the presence of fungal infection prior to the development of symptoms. This type of therapy may be more advantageous than prophylactic therapy, since overtreatment is avoided and treatment is targeted only to patients who actually have infection, but at an early stage. The feasibility of using preemptive therapy was recently examined by comparing outcomes with those obtained with empiric therapy. In patients with neutropenic fever, criteria for antifungal treatment resulted in 35% of patients being treated, while the preemptive approach (GM assay + high-resolution computed tomography [CT] scan) reduced the proportion of patients treated to 7.7% [30]. Furthermore, early initiation of antifungal treatment due to preemptive therapy occurred in 10 patients who would not have been suspected of having an IFI using the usual criteria for empiric therapy, namely persistent, unexplained fever [30]. Additional confirmation of the advantage of preemptive therapy using the GM assay and high-resolution CT scan was the finding that no seronegative patients developed aspergillosis [30]. Studies are currently under way to compare the efficacy of global prophylaxis with that of preemptive therapy combined with yeast prophylaxis.

Conclusion

Antifungal prophylaxis is a strategy that has proven effective against candidiasis and aspergillosis, the most common fungal infections in HSCT/bone marrow transplant recipients. The decision to use prophylaxis is dependent on a variety of treatment-related issues. One of the most important factors is conditioning regimen, which may predispose patients to specific types of fungal infections. For ablative conditioning regimens, yeast prophylaxis with fluconazole should be considered, as the risk for mucosal injury and neutropenia is elevated. Prophylaxis with extended-spectrum antifungal agents (itraconazole, micafungin, and posaconazole) to cover mold pathogens should be considered in HSCT recipients who receive cells from cord blood or T-cell–depleted grafts, as well as those who receive mismatched grafts, as these patients are at increased risk for mold infection. There exists controversy surrounding the use of broad-spectrum agents versus narrow-acting compounds such as fluconazole. Although broad-spectrum agents can noticeably reduce the number of cases of aspergillosis, clinical trial data often fail to show an improvement in overall mortality or failure rates, and adverse events may be more frequent. Therefore, patients placed on extended-spectrum agents still need to be monitored closely. Preemptive therapy—the administration of treatment to patients with documented infection before symptoms of the infection (eg, fever) become apparent—may represent a future option for the effective treatment of IFIs.

Clinical Considerations for Empiric and Preemptive Therapy

Dimitrios P. Kontoyiannis, MD, ScD, FACP

IFIs remain a serious issue in bone marrow transplant or HSCT recipients. Autopsy examination of patients with hematologic malignancies who underwent HSCT between 1989 and 2003 revealed that IFI rates remained constant at a rate of 20% to 25% and have attributable mortality of 80% (Figure 2) [10]. Prophylactic therapy is administered with the intention of preventing infection. However, persistent fever despite broad-spectrum antibacterials occurs not infrequently despite antifungal prophylaxis in high-risk patients. In such instances, it has been the standard of care to administer systemic antifungal agents upon the development of symptoms of a presumed IFI. Deciding about the need and type of effective empiric antifungal treatment has been complicated by the evolving and complex epidemiology of IFIs in the last 15 years. The most common IFIs are derived from molds such as *Aspergillus* species and yeasts such as *Candida* species. The occurrence of more resistant opportunistic fungi such as non-*fumigatus* strains of *Aspergillus* and non-*albicans* strains of *Candida* has slowly increased [10]. These data indicate a need for increased vigilance and need for knowledge of the local epidemiology regarding the specific species of infection, and also for determining which agents are most appropriate for each type of infection. Other considerations for optimal antifungal treatment are patient and pathogen factors. Strategies for bolstering the efficacy of current treatments are being investigated.

Risk Stratification and Antifungal Treatment

The Infectious Disease Society of America recommends the use of antifungal agents in patients who remain febrile after 5 or more days [31]. However, this approach should not substitute for careful clinical evaluation, since fever can have a variety of causes in the neutropenic patient population. Factors that further complicate empiric antifungal treatment decisions include heterogenous populations, immune defects, advanced age, comorbidities, inaccurate diagnostic tests, and the relative infrequency of IFIs. Selection of optimal antifungal treatment requires the consideration of

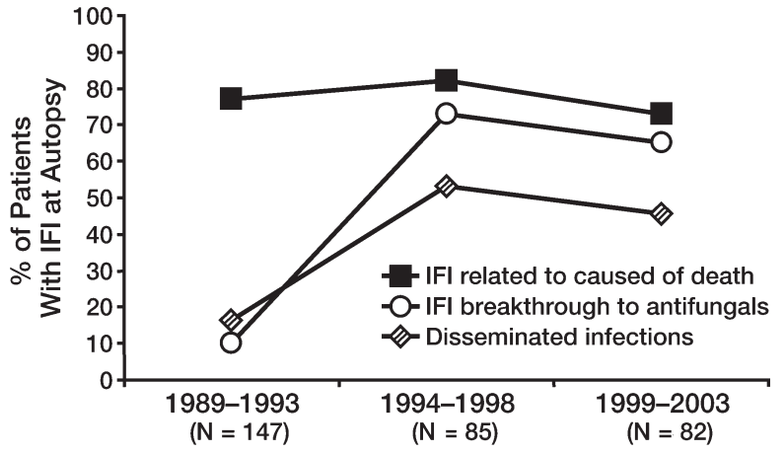

Figure 2. Rates of invasive fungal infections (IFI) and death between 1989 and 2003 in patients with hematologic malignancy [10].

Table 3. Factors to Consider for Successful Treatment of Invasive Fungal Infections*

Disease factors	Underlying disease
	Neutropenia/neutrophil recovery
	GVHD/steroids
	Mucositis
	Comorbidities
	Invasive devices
	Copathogens
Pathogen factors	Virulence factors
	Resistance
	Toxin production
	Immunodysregulation
	Host damage
Drug factors	Potency (MIC, MEC, MFC)
	Pharmacodynamics
	Pharmacokinetics

*GVHD indicates graft-versus-host disease; MIC, minimal inhibitory concentration; MEC, minimal effective concentration; MFC, minimum fungicidal concentration.

three important areas: host factors, pathogen factors, and drug factors (Table 3). In patients with suspected mycoses, individualized risk stratification, determination of the overall immunosuppressive state, qualitative and quantitative immune defects, and the site of infection are particularly important.

The indiscriminate use of antifungal prophylaxis for the prevention of IFIs has a number of disadvantages, including overmedicating patients (as only a small proportion of patients actually have an IFI), excessive cost, and risk for selection of resistance. Preemptive and empiric strategies are initiated when a patient has a reasonably high suspicion of having an IFI, as it has been shown that initiation of antifungal therapy early in the course of infection is associated with improved outcome. To that end, early use of chest CT scan for the identification of halo sign is a sensitive indicator of early invasive aspergillosis [7]. Subsequent early treatment has been shown to result in improved outcomes among patients with hematologic malignancy and neutropenia, as well as among allogeneic HSCT recipients, independent of agent used [7]. Specifically in the pivotal study by Herbercht et al, the number of patients with a satisfactory response rate (defined as a complete or partial global response) to voriconazole treatment increased when treatment was initiated when the halo sign was visible relative to when no halo sign was present (62.3% versus 41.5%, Figure 3) [7].Presence of the halo sign was also associated with more satisfactory responses in patients receiving amphotericin B (40.9% versus 15.8% when no halo sign was present, Figure 3) [7]. Presence of the halo sign is an important prognostic factor in patients with invasive aspergillosis, independent of agent used.

Diagnosis and Treatment of Antifungal Infection

There is an increasing need for diagnostics that yield results in real time and detect a broad spectrum of fungal pathogens from different sites of infection. The spectrum and dissemination of opportunistic fungal infections make the use of diagnostic tests difficult. Rare infections do occassionally occur: one example is *Fusarium*, which is resistant to caspofungin and fluconazole. It is also not uncommon for patients to have mixed infections. Traditionally, fungal culture has been the standard of diagnosis, although newer assays that are quicker and at least as accurate are being developed. Culture assays cannot always detect fungal infection in the presence of disseminated fungal tissue infection. Antigen detection assays and polymerase chain reaction (PCR) tests are often used in clinical trials and have good potential for widespread use after more rigorous validation has occurred. The disadvantage to antigen detection assays is the limited number of fungal species that can be detected. The GM assay is currently only able to detect aspergillosis [29]. The other well-known antigen detection assay for the detection of IFIs is for (1-3)-β-D-glucan, a component of the fungal cell wall [29]. The problem with the glucan assay is that it is nonspecific (ie, it can detect IFI caused by *Candida*, *Fusarium*, and *Aspergillus*) and has demonstrated an inability to detect zygomycosis [29]. PCR is one of the most promising future diagnostics, as it is designed to differentiate DNA from different species and strains while requiring only small amounts of fungal DNA samples (10-100 fg; equivalent to ~10-100 conidia/mL) [29].

The current choices for antifungal agents can be broken into 2 major groups based on the fungal target. Azoles and polyenes interrupt the integrity of the fungal cell membrane, whereas echinocandins target the fungal cell wall. In the empiric setting, the most commonly used agents are voriconazole, amphotericin B (lipid and nonlipid formulations), and caspofungin, all of which have similar overall survival rates (~90%) in patients with neutropenic fever [32-34]. Caution should be exercised when using the azole voriconazole in the empiric therapy setting, as prolonged use of this agent is associated with breakthrough zygomycosis [17,18]. Epidemiologic data from at least one institution has shown that since the introduction of voriconazole, the incidence of aspergillosis has decreased while zygomycosis is on the rise [17]. Diagnostic predictors of zygomycosis in patients receiving voriconazole treatment include pansinusitus/oral lesions, allogeneic bone marrow transplantation, a negative GM

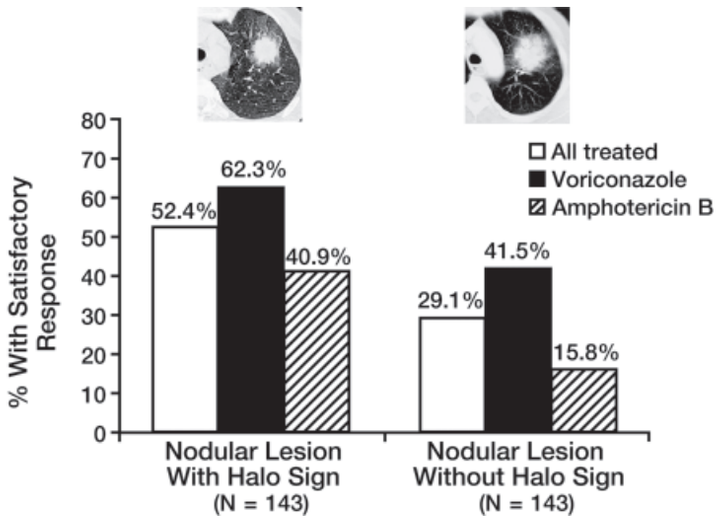

Figure 3. Percentage of hematologic oncology patients with invasive fungal infections achieving a satisfactory response as a function of halo sign [7].

assay, and ≥10 nodular lesions found upon chest CT scan [18]. Amphotericin B, a member of the polyene class of antifungal agents, has a broad spectrum of antifungal activity, but has a higher incidence of adverse events than either caspofungin or voriconazole. An important advantage of using the echinocandin caspofungin is that adverse events are rare, consisting primarily of abnormal liver function tests and histamine-like reactions [13,29,34]. Unfortunately, the utility of caspofungin is limited because of its lack of activity against fungal genera other than *Aspergillus* and *Candida*. When choosing a particular antifungal agent for empiric therapy, it is important to examine the disease status of each patient and determine prior antifungal exposure. None of the current antifungal agents are effective against all types of IFIs, and all have specific adverse events that need to be taken into account, so patients still need to be carefully monitored regardless of agent.

Strategies to Bolster the Efficacy of Antifungal Therapy

Several strategies are employed in an effort to enhance treatment efficacy in patients with refractory mycoses. A commonly used approach is to increase the dose of drug. In most cases, however, the implementation of this strategy is problematic, as the likelihood of toxicity (kidney or liver) increases with increasing doses of lipid amphotericin B and voriconazole respectively. Increasing the daily dose of posaconazole beyond 800 mg/d is ineffective because of dose-limited absorption. It is currently unknown whether increasing the dose of echinocandin agents, which are very safe even at high doses, is associated with increased efficacy. More appropriate methods for bolstering antifungal therapy include combination therapy, immunoaugmentation, surgery, and secondary prophylaxis. Although combination therapy is a commonly used strategy, it needs to be tested in an organized clinical trial setting. In a small retrospective single-center study in patients undergoing HSCT or receiving cytotoxic chemotherapy and in whom initial amphotericin B therapy for aspergillosis was ineffective, second-line therapy with the combination of voriconazole and caspofungin resulted in a higher 3-month survival probability than was seen in patients who received single-agent voriconazole (hazard ratio: 0.42, P = .04) [35]. When given to solid organ transplant recipients as primary antifungal therapy, the combination of voriconazole and caspofungin did not result in a significant difference in 3-month survival than was observed in patients who received lipid amphotericin B [36]. A small prospective study (n = 30) of patients with invasive aspergillosis examined the treatment efficacy of initial treatment with combination amphotericin B and caspofungin versus amphotericin B alone [37]. At the end of treatment (median duration of treatment: 18 days for combination and 17 days for monotherapy), 67% of patients receiving combination therapy had either a complete or partial response, compared with 27% for monotherapy (P = .028) [37]. Immune augmentation using cytokines or immune effector cells (granulocyte colony-stimulating factor–primed white blood cell transfusions) is thought to be a conceptually promising idea. The clinical data in support of this method are lacking, as most studies are both noncomparative and lacking in statistical power. For example, a case series described the effect of interferon γ and colony stimulating factor in 4 patients with leukemia and refractory candidiasis reported a clinical response in all patients, although 2 of the patients had a strong inflammatory reaction [38]. The results of these underpowered and uncontrolled reports indicate the need for more intense investigation, keeping in mind that patient selection and timing of intervention are key design issues for future studies. Surgery is another option that is overlooked. In some cases, fungal infection can lead to potentially fatal internal hemorrhaging that can only be treated with surgery. Lastly, in patients who have had prior IFIs, it is advisable to consider secondary prophylaxis to prevent recrudescence of the infection in the setting of intensification of immunosuppression in the face of recurrent disease.

Conclusions

The treatment of IFIs in transplant recipients has made strides in the last 15 years. There are a number of antifungal agents that can be employed. Azoles like fluconazole have led the way in the successful treatment and prevention of *Candida* infections. The successful treatment of candidiasis has likely played a contributory role in the shift from yeast to mold infections in transplant recipients. Azoles and echinocandins have resulted in a significant reduction in side effects compared with amphotericin B therapy, but more progress is needed. Currently, the biggest concern is to reduce the mortality associated with mold infections. The current group of broad-spectrum antifungals focuses on *A fumigatus*, although other molds need to be targeted as well. Agents such as posaconazole, which is active against a wide variety of molds in vitro and is able to reduce IFIs in transplantation patients [23]. In addition to the development of new agents, individualized treatment based on patient, host, and pathogen factors will be important for treatment optimization. A key component to improving treatment outcomes will be early detection and treatment through the development of non-culture–based diagnostics such as antigen detection assays (GM and glucan assays) and PCR. The largest hurdle for future antifungal treatment is a lack of understanding of the fundamental reasons for treatment failure. Does antifungal therapy fail because of resistance, host factors, drug pharmacokinetics, toxicity, an interaction with the underlying malignancy, or some combination of these factors? The significant decline in autopsies in recent years likely plays a role in the lack of understanding as to the causes of IFI-related treatment failure, autopsy remains the gold standard for determining the ultimate cause of death in a patient [10]. Once the reasons for treatment failure are better understood, it should be possible to treat even more successfully transplant recipients who have IFIs.

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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.

Tran N, Franken PR, Maskali F, et al: Intramyocardial implantation of bone marrow-derived stem cells enhances perfusion in chronic myocardial infarction: dependency on initial perfusion depth and follow-up assess by gated pinhole SPECT. J Nucl Med. 2007;48:405-412.

Direct implantation of bone marrow-derived stem cells (BMSCs) is being investigated as a means of enhancing perfusion in infarcted areas of myocardium. Although histopathologic studies show increased vessel density, the true impact on perfusion is unknown. Changes in myocardial perfusion in areas treated with BMSCs were investigated using an original pinhole single-photon emission computed tomography (SPECT) technique.

Chronic myocardial infarction was induced in rats, one group of which were treated by intramyocardial injection of ^{111}In-labeled BMSCs. A dual ^{111}In/^{99m}Tc pinhole-SPECT technique was used to evaluate distribution of the radiolabeled stem cells within the targeted area after 48 hours. At intervals up to 3 months, serial assessments of myocardial perfusion were made using ^{99m}Tc-sestamibi pinhole gated SPECT.

At 48 hours' follow-up, all treated rats showed ^{111}In-BMSCs in the targeted area of myocardium. This included 18 or 32 segments previously shown to be underperfused, based on less than 70% sestamibi uptake on pretransplant scans. Over the next 4 months, perfusion of infarcted segments decreased in untreated rats, with an absolute mean decrease of 3% in sestamibi uptake. In contrast, BMSC-treated animals showed a 4% increase in sestamibi uptake. The degree of improvement was not significantly related to initial deposition of ^{111}In-BMSCs. However, it was substantially higher in areas with initially less severe perfusion defects: a mean increase of 6% in segments with 60% to 70% sestamibi uptake, compared with a 1% decrease in segments with less than 60% uptake.

Intramyocardially injected BMSCs are well-retained in infarcted segments in this rat model of chronic myocardial infarction. At longer-term follow-up, perfusion is significantly increased in areas that had relatively good residual perfusion before treatment—improvement does not necessarily occur in areas with good initial cell engraftment. The effects of intramyocardial BMSC treatment appear to depend on perfusion and metabolic environment of the implantation sites.

Natzke AM, Shaw JL, McKeller MR, et al: Hematopoietic stem cell recipients do not develop post-transplantation immune tolerance to antigens present on minimal residual disease. Biol Blood Marrow Transpl. 2007;13:34-45.

In patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) for leukemia or lymphoma, posttransplant immunologic processes are involved in both the graft-versus-leukemia (GVL) effect and graft-versus-host disease (GVHD). The authors have been investigating the use of posttransplant tumor vaccines in mice to enhance GVL effects without increasing GVHD. In this model, the absence of GVHD in response to vaccination may reflect gradual development of tolerance or unresponsiveness to recipient immunodominant minor histocompatibility antigens. The current study sought to determine whether similar unresponsiveness also develops to antigens present on minimal residual disease.

The HSCT model used C3.SW female donors and C57BL/6 female recipients, matched for major histocompatibility complex but mismatched for minor histocompatibility complex. As a model of minimal residual disease, recipients were vaccinated with male C57BL/6 leukemia/lymphoma cells, which contained an immunoglobulin/c-myc oncogene. The recipients were followed up for development of unresponsiveness to antigens present on small numbers of leukemia/lymphoma cells.

After transplantation, the recipients showed no immune response to the immunodominant recipient strain H7 minor histocompatiblity antigen, which was widely expressed in recipient tissues. However, there was a significant T-cell response to the well-characterized male HY antigen system, which was present only on small numbers of HY+ tumor cells at the time of transplantation. Similar anti-HY responses were noted in further studies using other models of minimal residual disease: nonmalignant recipient male B cells or dendritic cells.

Allogeneic HSCT recipients do not appear to develop immunologic unresponsiveness to antigens present on minimal residual disease. Despite the ability to mount a T-cell response to these antigens, recipients may still develop tolerance to the more widely distributed immunodominant minor antigens that contribute to the development of GVHD. The findings support a possible role of posttransplant vaccination as a means of enhancing control of minimal residual disease.

Jedema I, Meij P, Steeneveld E, et al: Early detection and rapid isolation of leukemia-reactive donor T cells for adoptive transfer using the IFN-γ secretion assay. Clin Cancer Res. 2007;13:636-643.

Donor lymphocyte infusion is commonly tried in patients who have persistent or recurrent leukemia after allogeneic stem cell transplantation. However, its effectiveness is limited by the low immunogenicity of most leukemias and the lack of specificity of nonselected donor lymphocytes. Adoptive transfer of in vitro-generated leukemia-reactive T-cells may be useful in this situation, although previous reports have questioned the reproducibility of this procedure, as well as the persistence and survival of the transferred T cells. A new and efficient approach to generation and isolation of leukemia-reactive T cells is reported.

The investigators used various disease-specific strategies to modify leukemic cells into "professional" antigen-presenting cells (APCs). The malignant APCs were then used to stimulate HLA-matched donor T-cells. After two stimulations, an assay was used to identify T cells that responded to the APCs by producing interferon (IFN)- γ. The cells were then tested for cytotoxicity against the primary leukemia.

Phenotypically appropriate APCs were developed for four types of leukemic cells. Using one general stimulation and isolation protocol, the researchers were reproducibly able to generate T-cell populations with high frequencies (8% to 53%) of leukemia-reactive T cells. Most of the cytotoxic T-cell clones produced IFN-γ in response to stimulation with the leukemia. The isolated T cells retained high proliferative potential, with reactivity only against cells of the patient's hematopoiesis.

The new approach is a promising one for isolation of leukemia-reactive T cells for the treatment of patients with relapsed leukemia after allogeneic stem cell transplantation. The technique reproducibly produces cells with hematopoietic specificity and residual proliferative capacity. In vivo survival and expansion of the T cells is likely promoted by their isolation at an early stage in the immune response and their short period of culture in vitro.

Ballen KK, Spitzer TR, Yeap BY, et al: Double unrelated reduced-intensity umbilical cord blood transplantation in adults. Biol Blood Marrow Transpl. 2007;13:82-89.

Umbilical cord blood (UCB) has proven to be a useful source of stem cells for patients who lack matched related or unrelated donors. However, because of a high rate of transplantation-related mortality, the results have not been as favorable in adults as children. Most of these deaths are related to slow engraftment or failure to achieve immunocompetence. An alternative approach using reduced-intensity conditioning followed by two partially matched UCB units was tested for its ability to increase cell dose with reducing transplantation-related toxicity.

The study included 21 adult patients, median age 49 years, who had acute myeloid leukemia, non-Hodgkin's lymphoma, or other diagnoses with no suitable matched donor. The reduced-intensity conditioning regimen consisted of fludarabine, melphalan, and antithymocyte globulin. This was followed by sequential infusion of two partially matched UCB units—a 4/6 HLA match or better with each other and with the patient. In each case, the cell dose before cryopreservation was 3.7×10^7 nucleated cells/kg.

There were two cases of primary graft failure requiring a second UCB procedure, and one case of late graft failure. An absolute neutrophil count of greater than 0.5×10^9/L was reached in a median of 20 days and an unsupported platelet count of greater than 20×10^9/L in 41 days. There was a 40% rate of grade II to IV acute graft-versus-host disease (GVHD); at 100 days, transplant-related mortality was 14%. At 1 year, overall survival was 71% and disease-free survival 67%. Patients with mixed chimerism had a higher rate of chronic GVHD.

A regimen using reduced-intensity conditioning followed by double UCB transplantation yields promising results in adult patients without sibling donors. In the authors' experience, the regimen is well tolerated and produces long-term antitumor responses with low transplant-related mortality.

Xu L, Duan L, Cao K, et al: Predominant immature CD8α⁺ dendritic cells prevent graft-vs.-host disease but do not increase the risk of leukemia recurrence. Eur J Hematol. 2007;78:235-245.

Graft-versus-host disease (GVHD) and recurrent leukemia are two major complications of allogeneic bone marrow transplantation (BMT) and stem cell transplantation. There is a need for new approaches to preventing or managing GVHD while preserving the graft-versus-leukemia effect of transplantation. This study evaluated the effects of predominant CD8α⁺ immature dendritic cells in vitro and in vivo.

The investigators employed a previously described technique using granulocyte-macrophage colony-stimulating factor, interleukin-4, stem cell factor, and Flt3L to generate dendritic cells from mouse bone marrow cells. The suppressive effects of these cells were investigated in vitro as well as in a mouse model of allogeneic BMT for leukemia.

Morphologically and phenotypically immature CD8α⁺ dendritic cells were demonstrated on the third day of culture. In vitro, the cells showed weak syngeneic stimulating effects on lymphocytes, with the ability to suppress mixed leukocyte reactions. In the allogeneic BMT model, the cells prevented the development of severe GVHD while prolonging the survival of recipient animals. There was a dose-dependent relationship between the number of CD8α⁺ dendritic cells infused and the prevention of GVHD—87% of mice receiving 1 million CD8α⁺ dendritic cells achieved long-term survival, with no increase in the leukemia recurrence rate.

Immature CD8α⁺ dendritic cells are potentially useful for reducing the risk of GHVD after allogeneic BMT. In these in vitro and in vivo studies, the cells show significant suppressive and tolerogenic effects without increasing the risk of recurrent leukemia. Further study is needed to evaluate their role in the clinical treatment of GVHD.

Kakinuma S, Asahina K, Okamura K, et al: Human cord blood cells transplanted into chronically damaged liver exhibit similar characteristics to functional hepatocytes. Transpl Proc. 2007;39:240-243.

Previous studies have suggested that cord blood cells transplanted into an injured liver exhibit hepatocyte-like phenotypes. However, few studies have been performed to characterize these hepatocyte-like cells (HLCs). The characteristics of cord blood cells transplanted into injured livers were analyzed in detail.

Human cord blood cells were transplanted into the livers of mice with transient liver or chronic liver damage. The development of HLCs was documented, and their expression of hepatic differentiation markers was analyzed.

In NOD/SCID mice with transient liver damage, HLCs were widely distributed but present at only a low frequency in the 3 weeks after cord blood cell transplantation. In contrast, higher numbers of HLCs were found in the livers of SCID mice with chronic liver damage caused by a urokinase-type plasminogen activity transgene under the control of albumin promoter/enhancer. In both types of liver injury,

the HLCs expressed only a few human hepatocyte markers. However, cytochrome P450s and other transcripts associated with mature hepatic functions were found only in the model of chronic liver injury.

Cord blood cells transplanted into the liver can develop into HLCs with characteristics similar to those of functional hepatocytes. Engraftment appears to be more efficient in the setting of chronic liver damage, as opposed to transient liver injury. Although further study is needed, cord blood may provide a new source of transplantable cells for use in the treatment of decompensated liver disease.

Asavaroengchai W, Wang H, Wang S, et al: An essential role for IFN-γ in regulation of alloreactive CD8 T cells following allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transpl. 2007;13:46-55.

Interferon (IFN)-γ appears to play a key role in inducing cellular immune responses. In previous studies using fully major histocompatiblity complex-mismatched bone marrow transplantation, the authors found that CD8 T cells from IFN-γ knockout donors lead to more severe graft-versus-host disease (GVHD) than do CD8 cells from wild-type donors. Further experiments were performed to clarify the mechanisms by which IFN-γ reduces the development of GVHD after allogeneic hematopoietic cell transplantation (HCT).

The study used a clinically relevant parent → F1 (B6 → B6DF21), haplotype-mismatched model of allogeneic HCT. As in the previous experiments, some mice received cells from IFN-γ gene knockout donors and others from wild-type donors. The development of GVHD was assessed by histopathologic examination and T-cell effects by flow cytometry.

Lethal GVHD with severe lung and liver injury developed in mice receiving CD4-depleted splenocytes from IFN-γ-deficient mice, whereas recipients of cells from wild-type mice had long-term survival. After transplantation, CD8 T cells from IFN-γ knockout donors showed rapid activation followed by accelerated cell division and reductions or delays in activation-induced cell death. This led to significantly increased numbers of activated and effector cells—including CD25+, CD62L–, and $CD44^{high}$—compared to recipients from wild-type donors.

Interferon-γ plays a key role in regulating alloreactive CD8 T cells after allogeneic HCT. It inhibits activation and expansion of donor CD8 cells by blocking cell division and promoting cell death, leading to promotion of graft-versus-leukemia effects and inhibition of graft-versus-host effects. Further studies of IFN-γ effects on T-cell reactivity may lead to new approaches to the prevention and treatment of GVHD.

Kato K, Kanda Y, Eto T, et al: Allogeneic bone marrow transplantation from unrelated human T-cell leukemia virus-I–negative donors for adult T-cell leukemia/lymphoma: retrospective analysis of data from the Japan Marrow Donor Program. Biol Blood Marrow Transpl. 2007;13:90-99.

The peripheral T-cell neoplasm adult T-cell leukemia/lymphoma (ATLL), caused by human T-cell leukemia virus type I (HTLV-1), carries a very poor prognosis. Good responses to allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an HLA-matched related donor have been reported, but matched dibbling donors are often not available. The Japanese experience with unrelated bone marrow transplantation for ATLL is reviewed.

The analysis included Japan Marrow Donor Program data on 33 patients who underwent UBMT for ATLL between 1999 and 2004. The patients were 18 men and 15 women, median age 49 years; UBMT was performed a median of 8 months after diagnosis. The extent of HLA matching varied, but all donors were negative for HTLV-I.

Five recipients died within 20 days—the remaining 28 achieved neutrophil engraftment. There was a 61% incidence of grade II to IV acute graft-versus-host disease (GVHD), while chronic GVHD developed in 4 of 18 patients. At 1 year, overall survival was 49.5% and progression-free survival 49.2%. The cumulative incidence of disease progression was 18.6%, with a 32.3% incidence of progression-free mortality. On multivariate analysis, age was the only factor independently associated with overall survival. The risk of treatment-related death was higher for patients who were over age 50 and not in remission at the time of UBMT.

For patients with ATLL who lack an HLA-matched sibling donor, allo-HSCT from an unrelated donor negative for HTLV-I is a viable treatment option. Treatment-related mortality is a significant problem, especially for older patients not in remission. The authors call for controlled trials to clarify the efficacy of and indications for this approach.

Insights Into Early Empiric or Prophylactic Antifungal Therapy in a Transplant Setting

CME Assessment Test

1. **Which of the following antifungal agents functions through disruption of the fungal cell wall?**
   A. Amphotericin B
   B. Caspofungin
   C. Posaconazole
   D. Voriconazole

2. **Which of the following represents a low-risk situation for the development of candidiasis in hematopoietic stem cell transplant (HSCT) recipients?**
   A. Autologous transplant
   B. Conditioning regimens that produce neutropenia
   C. Conditioning regimens that result in mucosal injury
   D. Nonmyeloablative conditioning regimens
   E. A+B
   F. C+D

3. **The prophylactic use of voriconazole in HSCT recipients has been shown in the literature to be associated with which of the following?**
   A. An increase in serious adverse events when administered to neutropenic patients
   B. Breakthrough zygomycosis
   C. Toxic drug interaction with cyclophosphamide
   D. All of the above
   E. None of the above

4. **The prophylactic use of broad-spectrum antifungal agents (such as itraconazole, posaconazole, or caspofungin) is not generally associated with an increase in overall survival compared with fluconazole prophylaxis.**
   A. True
   B. False

5. **Which of the following is not a risk factor for developing aspergillosis after HSCT?**
   A. Myeloablative conditioning
   B. Nonmyeloablative conditioning
   C. Use of T-cell–depleted stem cell transplants
   D. All of the above
   E. None of the above

6. **The use of rapid diagnostics, specifically the galactomannan assay, is especially useful for which type of fungal treatment?**
   A. Empiric
   B. Preemptive treatment
   C. Prophylaxis
   D. A+C
   E. B+C

7. **Which of following is one of the most important prognostic indicators for survival of HSCT recipients when using empiric therapy?**
   A. Halo sign upon computed tomography (CT) scan of the lung
   B. Low leukocyte values
   C. Positive galactomannan test
   D. Presence of mucositis

8. **The biggest advantage of using polymerase chain reaction (PCR) as a tool for the diagnosis of invasive fungal infection is**
   A. Cost
   B. Ease of use
   C. Speed of assay
   D. Specificity

9. **All of the following agents would be acceptable to use against aspergillosis except**
   A. Amphotericin B
   B. Caspofungin
   C. Fluconazole
   D. Posaconazole
   E. Voriconazole

10. **Which of the following has shown the least benefit in terms of efficacy and safety when trying to enhance antifungal treatment?**
    A. Combination therapy
    B. Dose increase
    C. Immune augmentation
    D. Surgery

CME Assessment Test Answer Sheet

Release Date: May 31, 2007 **Last Review Date: May 31, 2007** **Expiration Date: May 31, 2008**

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 Medical Education, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. No processing fee is required.

1.	A	B	C	D			**5.**	A	B	C	D	E		**9.**	A	B	C	D	E
2.	A	B	C	D	E	F	**6.**	A	B	C	D	E		**10.**	A	B	C	D	
3.	A	B	C	D	E		**7.**	A	B	C	D								
4.	A	B					**8.**	A	B	C	D								

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Overall quality of the CME activity	1	2	3	4	5
Articles in the publication were presented in a clear and effective manner	1	2	3	4	5
The material presented was current and clinically relevant	1	2	3	4	5
Educational objectives were achieved	1	2	3	4	5
The CME activity provided a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias	1	2	3	4	5

Please comment on the impact (if any) that this CME activity might have on your management of patients.

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