BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 0101 FREQUENTLY ASKED QUESTIONS (FAQs)

A Randomized Double-blind Trial of Fluconazole vs. Voriconazole for the Prevention of Invasive Fungal Infections in Allogeneic Blood and Marrow Transplant Patients

1. HOW DO I ESTABLISH THE DIAGNOSIS OF INVASIVE FUNGAL INFECTION?

The criteria are specified in Table 3.1.1 of the protocol. These definitions were established by a consensus panel of the EORTC and MSG using published studies of invasive fungal infections. For the endpoint, the criteria for proven or probable infection must be met. "Possible" fungal infection is not a study endpoint, but does permit use of empirical amphotericin B if the clinician feels it should be done while diagnostic testing proceeds. For both possible and probable infection the host factor criterion must be present; the difference is that for probable, both one of the clinical **and** microbiological criteria must also be present while for possible infection, either one of the microbiologic **or** clinical criteria must be present.

What if I am not sure how to interpret the table?

After the site enters the patient's fungal infection data on the "Fungal Infection" (FIN) case report form (CRF) via the Internet Data Entry System (IDES), a computer algorithm will be run and provide the site with feedback the next day.

But, I still am confused…?

Call the medical monitor (Dennis Confer**,** 612-362-3425) or protocol coordinator (Iris Gersten, 301-251-1161). We are available to answer your questions.

2. ARE THERE SPECIAL CONSIDERATIONS WHEN MONITORING THE IMMUNOSUPPRESSION IN PATIENTS ON THE TRIAL?

It is important to note that both study drugs increase levels of cyclosporine and tacrolimus. Thus, it is important that the blood levels of these immunosuppressive drugs be checked in patients on the study. There is a difference in the magnitude of potentiation caused by voriconazole and fluconazole. Voriconazole raises the levels to a greater degree than fluconazole. **It is important that concentrations of the cyclosporine or tacrolimus (and creatinine) be checked frequently especially during the first two weeks of the study**. **We recommend checking the blood levels at least three times weekly and adjusting the cyclosporine or tacrolimus doses accordingly.**

If there are differences between fluconazole and voriconazole in affecting the cyclosporine or tacrolimus levels, will I be able to tell which drug the patient is on?

There is such variability in a given dose producing a given concentration that even if the absence of either study drug, dose adjustments of cyclosporine or tacrolimus are frequently needed. Similarly, there is substantial overlap between the range of effects of either study drug that it is unlikely that one can confidently predict the patient's study drug assignment.

3. WHAT IS THE GALACTOMANNAN ASSAY?

The galactomannan assay is a blood test that can be useful in the detection of aspergillus infection. Galactomannan is a substance that is released into the bloodstream of patients with aspergillus infection. When the quantity of galactomannan is sufficiently high enough it can be an indicator of aspergillus infection. The test result will be "positive" or "negative." **By itself a positive test does not prove infection.** In combination with appropriate clinical test findings and in certain patient conditions, it can indicate a probability of infection. A positive test result should prompt the clinician to repeat the test (draw another sample and send it along with the next scheduled specimen to be collected) and to perform additional clinical testing for more definitive evidence of fungal infection.

Can the patient be infected in the absence of a positive test?

Yes. The **test detects only aspergillus** and does not detect other clinically important fungi. Moreover, there is the possibility that aspergillus infection may be present in the absence of a positive test. If a patient has clinical symptoms or signs suggestive of infection, diagnostic testing should be pursued even if the test is negative.

What should I do if my patient has a positive test?

It is very important to perform a full range of diagnostic testing, just as one would do if one did not have this test. This will include fungal blood cultures, CT scans, bronchoscopy of pulmonary infiltrates, cultures and biopsies of suspected sites of infection. **A positive galactomannan test by itself should not constitute grounds for instituting antifungal therapy**. If the patient has sufficient evidence for fungal infection that meets the definition of "possible" fungal infection as defined in Table 3.1.1 in the protocol, a trial of empiric amphotericin B may be instituted while diagnostic testing is performed.

How often should I test my patient?

It is recommended that the galactomannan (GM) assay be used as a surveillance tool twice weekly during the HSCT patient's at risk period (day 0 to day 60-100 post transplant). For this study, diagnostic GM blood samples should be collected twice weekly on two non-consecutive days, preferably 3 days apart (e.g., Mondays and Thursdays), during the first 60 days post transplant and once weekly on days 60-100 unless one of the following criteria is met: (1) patient received a T cell depleted transplant and received post-transplant GVHD prophylaxis or (2) patient is on steroids or (3) patient has or has had acute GVHD. Diagnostic GM samples should be collected twice weekly from these select patients. In addition, diagnostic GM samples should be collected prior to and at the onset of possible fungal infection and twice weekly from patients receiving empiric trials of amphotericin B for possible infection.

In addition, a baseline GM sample must be collected up to one week prior to the start of the conditioning regimen. If the results of the baseline galactomannan assay are not available prior to the initiation of conditioning, a CT scan of the chest is required.

How should I collect the GM sample?
On each scheduled collection day, one 5 ml peripheral blood sample (2.5 ml for pediatric patients less than 12 years old) should be collected in a gold top plastic serum separator tube (BD# 367986 for adults, BD# 367983 for pediatric patients), centrifuged, but not decanted or transferred. It should then be cold-packed and shipped priority overnight for "next morning delivery" to a certified reference laboratory.

What reference labs conduct the Diagnostic GM Assay?
The Diagnostic GM assay may be performed by: (1) the University of Washington Community Laboratory Services (http://depts.washington.edu/labweb/cs/csohome.html, 800-713-5198), (2) a certified contract laboratory or (3) a certified hospital laboratory associated with the transplant center. "Certified" refers to CLIA, CAP or JCAHO certification. It is recommended that laboratories complete Bio-Rad's proficiency panel and use the criteria for galactomannan positivity as defined in §3.2 of the protocol; i.e., two consecutive positives (index value $\geq$ 0.5) on one sample.

What are the Monitoring of Treatment GM Samples?
One of the secondary endpoints to be evaluated in this study is the utility of the galactomannan assay to determine response to therapy. Accordingly, even if the patient develops a probable or proven invasive fungal infection, twice weekly Monitoring of Treatment GM samples should be collected at onset and after initiation of treatment for the infection for four weeks, then once every two weeks for eight weeks for a total of 12 samples. These samples will be frozen and batch shipped to the Repository. The assays will be performed after completion of study enrollment at Fred Hutchinson Research Cancer Center (FHCRC). The investigators will be blinded to the results.

4. ARE EMPIRIC TRIALS OF AMPHOTERICIN B PERMITTED IN THE TRIAL?
Yes. Empiric amphotericin B can be used in patients with suspected fungal infections while clinical testing is being conducted. This is an important safety provision. But they are restricted to certain situations where there is sufficient evidence for fungal infection. For neutropenia before engraftment, the patient has to have persistent fever despite broadspectrum antibiotics without an infection being identified for at least 96 hours. After engraftment, the patient has to meet the criteria for "possible" fungal infection specified in Table 3.1.1. The conditions for justification for starting a trial of empiric amphotericin B are described in §2.4.10 of the protocol.

Are there any requirements during amphotericin B trials?
Yes. First, a repeat blood sample for galactomannan should be collected before starting amphotericin B. Second, the amphotericin B trial should be justified by the protocol criteria in Table 3.1.1: at least one host criterion **plus** either one microbiological criterion **or** one major (or two minor) clinical criterion. Third, the purpose of the trial is to allow you time to perform a complete evaluation and get the results back. If the results are negative, you should stop the empiric trial. If the results are positive and the patient is confirmed to have a "probable" or "proven" fungal infection, the endpoint is reached. Fourth, galactomannan assays should still be performed twice weekly during the evaluation. Fifth, the study drug should be continued.

What are the limits on empiric amphotericin B use?
It should only be used, as noted above, to allow evaluation to proceed. In no case should it continue beyond 14 days. In most cases it will need to be given for only several days to allow testing and receive the results.

What do I do with the study drug while empiric amphotericin is being given?
It is to be continued. Both amphotericin B and the study drug cannot be given together more than 14 days. One or the other must be stopped after 14 days as specified in the protocol.

5. HOW DO I GO ABOUT MAKING A DEFINITIVE DIAGNOSIS OF A PULMONARY INFILTRATE?

A good first step for the patient with a pulmonary infiltrate is the performance of the galactomannan assay and CT scan. This should be followed by performance of a bronchoscopy with BAL and biopsy (if deemed to be safe) or percutaneous needle biopsy for peripheral nodules (or both in turn if necessary).

If the diagnosis is not confirmed by these procedures, then you should consider an open lung biopsy to establish a firm diagnosis. There are obvious pros and cons with an open biopsy. There is more morbidity and sometimes the patient may not be a suitable candidate for it. On the positive side, it remains the gold standard for diagnosing pulmonary aspergillosis. A firm diagnosis will allow you to eliminate some potentially toxic empiric therapies which frequently are required when you cannot be sure of what you are treating, and surgical excision can be therapeutic as well as diagnostic in the case of aspergillosis. It is important to note that while BAL has an excellent yield for certain pathogens (e.g., CMV, PCP), the yield for aspergillus is poor. Additional testing is frequently required to firmly establish or refute the diagnosis.

6. WHAT HAPPENS WHEN MY PATIENT REACHES THE PRIMARY ENDPOINT (I.E., PROBABLE OR PROVEN INFECTION)?

In the event of the patient demonstrating a probable or proven invasive fungal infection as per the criteria specified in Table 3.1.1, the patient has reached the primary study endpoint, should stop study drug and the clinician is free to treat the infections according to local institutional guidelines. The following are offered as suggestions.

One option is to use amphotericin B and voriconazole together. This would provide adequate therapy for most fungal pathogens irrespective of which study drug the patient was assigned to and this strategy would ordinarily not require breaking the blind. Voriconazole is to be given at a dose of 6 mg/kg/dose IV twice daily for two days, then at a dose of 4 mg/kg/d thereafter. One can switch to the equivalent dose orally once the patient is stable and taking oral drugs satisfactorily. The dose of amphotericin B is 1.0 mg/kg/d if the conventional formulation is used or is 4.0-5.0 mg/kg/d if a lipid formulation is used. If the pathogen is mucormycoses, an amphotericin B formulation is the therapy of choice; voriconazole is not active against this pathogen and is not needed.

For patients with proven mucormycoses or probable fungal infection with filamentous fungal forms on cytologic or histologic section which cannot exclude mucormycetes, an amphotericin B

formulation (or other investigational therapy) is recommended. Voriconazole is not active against mucormycosis.

Can I break the blind once the patient has reached primary endpoint?
No. Study drug assignment may be revealed only for reasons relating to the patient's safety or when critical therapeutic decisions are contingent upon knowing the assigned study drug. A decision to break the blind must be discussed with the medical monitor in advance. Withdrawal of a patient from the study treatment is not a sufficient reason to break the study blind.

7. WHAT CIRCUMSTANCES PROMPT EARLY WITHDRAWAL OF STUDY DRUG?
Patients will be withdrawn from study drug if they meet any ONE of the conditions below:

- There is evidence at any time during the study of a probable or proven invasive fungal infection as defined by criteria in §3.1.1 of the protocol (see question #6 above).
- Any of the following toxicities occur. However, if another etiology is judged by the local PI to be the likely cause of the toxicity and an interval of no more than 10 days has lapsed, then the study drug can be resumed at original dose. If the same toxicity recurs, the patient will be withdrawn from the study treatment.

    a) For hepatic toxicity: If ALT exceeds ten times the upper limit of normal and is felt to be at least possibly related to study drug, the study drug should be held until the causality clarifies and until the toxicity resolves to a Grade II or less.

    b) For visual toxicity: Photopsia (visual disturbances) is an occasional side effect of voriconazole. It typically is transient and is not associated with organic or enduring sequelae. It does not represent grounds for withdrawal. If a patient experiences loss of vision (blindness), it is unlikely that it is due to the study drug; however, the study drug should be held until etiology is established. Cyclosporine and tacrolimus can cause loss of vision and should be held. Retinal hemorrhage is also a potential cause of visual loss and platelet transfusions and optimization of coagulation parameters should be considered where appropriate. Ophthalmic evaluation should be promptly carried out.

    c) For cutaneous toxicity: A skin rash can occasionally occur. This may be provoked or exacerbated by sun exposure. Other potential causes of rash should be investigated, including graft-versus-host disease and drug sensitivity. A skin biopsy may be useful in the evaluation of other causes. This ordinarily will not constitute grounds for withdrawal unless there is skin necrosis or ulceration or generalized exfoliative dermatitis.

    d) For neurologic toxicity: An infrequent observation in patients receiving voriconazole is hallucinations. A preliminary analysis suggests this is due to potentiation of opiate or benzodiazepine effect. If such should occur, attempts should be made to reduce opiate and/or benzodiazepine dosages. If necessary after at least 24 hours after reduction of the dose(s) of concomitant opiates or benzodiazepines, study drug can be held (without withdrawal) up to 10 days as specified above to allow reduction of doses of these concomitant medications.

e) For cardiac arrhythmia: If a significant arrhythmia occurs, study medication must be held, and the subject must undergo further assessment by a cardiologist to evaluate the significance of the findings. The cardiologist's assessment and opinion on the significance of any abnormal finding will be summarized in a report and submitted with an Adverse Event Form. If the PI and cardiologist conclude that it is not related to the study drug, study drug can be resumed as specified above. Otherwise, the patient will be withdrawn from study treatment.

f) For renal insufficiency: The patient experiences serious renal impairment requiring hemodialysis.

g) For any other Grade III or IV toxicity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 which is not typically expected in the course of BMT and may be possibly related to study drug.

- Systemic amphotericin B (or one of the lipid formulations) is given for more than 14 consecutive days.
- The patient requires terfenadine, astemizole, cisapride or sirolimus, maintenance phenytoin/anticonvulsant therapy, or any of the drugs prohibited at study entry (§ 2.3.2).
- The patient is an outpatient and requires IV study drug for more than 14 consecutive days and cannot tolerate oral study drug. **Please note that IV study drug must be prepared by the investigational pharmacist (and not by home health care) in order to maintain the study blind**.
- The patient becomes pregnant.
- The patient withdraws consent.

The medical monitor should be contacted for advice about any of the above considerations for holding or withdrawal of the study drug due to adverse events.

What assessments are required when study drug is discontinued?
When study drug is discontinued **for any reason** including probable or proven infection, the following must be completed **in addition to all study assessments required through Day 365**:

- A physical examination including vital signs should be performed within 72 hours of discontinuing study drug.
- If previously positive, CT scans of chest, abdomen or sinus should be performed within a 72-hour window of study drug discontinuation; and if an abnormality suspected or proven to be fungal in nature is still present, pertinent studies should be repeated approximately two weeks following study drug completion and subsequently repeated until resolution of clinical or radiographic signs of infection, generally at no more than 6 week intervals.
- Other follow-up diagnostic tests should be obtained as deemed appropriate by the principal investigator.
- Blood sample (5 ml for adult patients, 2.5 ml for pediatric patients less than 12 years old) should be obtained for pharmacokinetic analysis of fluconazole or voriconazole concentrations (as per Appendix C).

- All study drug withdrawals should be reported on the "Permanent Study Drug Withdrawal" case report form via the Internet Data Entry System within three business days.

8. HOW IS THE PATIENT'S TREATMENT ASSIGNMENT COMMUNICATED TO THE SITE?

The clinic coordinator at the transplant center will complete the patient's initial screening by entering demographics, segment 0 information (date informed consent was signed) and segment A information (inclusion/exclusion criteria and HLA typing) of the eligibility form via the Internet Data Entry System (IDES) within one week prior to initiation of the conditioning regimen. If the patient is eligible, an ALT test must be obtained within 72 hours of the transplant (day 0). The coordinator then completes the enrollment process by entering the results of the ALT test on segment B of the eligibility form via the IDES within 72 hours of transplant. If the patient is eligible, a random treatment assignment number is immediately generated. The coordinator is responsible for forwarding the randomization number to the investigational pharmacist. The investigational pharmacist will use the code list provided at the beginning of the study to decode the number and prepare the appropriate study drug. **The investigational pharmacist will be the only unblinded staff member at the transplant center and is required to maintain the blind.**

9. WHY MUST I REGISTER ALL OF MY TRANSPLANT PATIENTS INCLUDING THOSE NOT PARTICIPATING IN BMT CTN PROTOCOLS WITH THE IBMTR?

The data collection system and monitoring system for BMT CTN trials builds on the IBMTR data collection system. An essential part of this process is registration of ALL patients transplanted in each participating center. This requires completion of the IBMTR "Pre-Reg Form". **Registration of transplant recipients (both those entered and those not entered on BMT CTN trials) is a requirement for all Core and non-Core centers.** These data will be used to generate recruitment reports that would otherwise be requested of each center monthly to meet NHLBI recruitment monitoring requirements. They will also be used to study the recruitment process and evaluate ways in which we can modify protocols or institute other measures to enhance accrual to BMT CTN protocols.

What forms must I submit to the IBMTR?

- **Pre-Registration Form** for ALL patients **(**both those entered and those not entered on BMT CTN trials) is a requirement for all Core and non-Core centers. At a minimum, these must be batched **monthly** to the IBMTR**.**
- **TED Form** (including the Core, Graft and Disease inserts) at 100 days post transplant for all patients enrolled in BMT CTN protocols. At a minimum, these must be batched **quarterly** to the IBMTR.
- **Follow-up TED Form** (including the Core and Disease follow-up inserts) yearly for all patients enrolled in BMTCTN protocols. At a minimum, these must be batched **quarterly** to the IBMTR.

How do I submit the IBMTR forms?

You may submit "paper" or "electronic" IBMTR forms directly to the IBMTR as you currently do. If you chose to submit paper forms, green "BMT CTN" stickers will be provided to you to place on the forms to notify the IBMTR that your center is participating in BMT CTN protocol(s).