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AN ADAPTIVE BAYESIAN DESIGN FOR A RANDOMIZED TRIAL OF HIGH- VERSUS LOW-LEVEL TACROLIMUS AS PROPHYLAXIS FOR GRAFT-VERSUS-HOST DISEASE IN ALLOGENEIC STEM CELL TRANSPLANTATION

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We describe a Bayesian adaptive design for a randomized phase II/III clinical trial to compare 2 different tacrolimus (FK506) blood levels for the prevention of graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation. The scientific objectives are to estimate differences in overall survival, regimen-related mortality, acute GVHD, and toxicity at high (8–12 ng/mL) versus low (4–6 ng/mL) tacrolimus blood levels, and to estimate the rates of these events within each treatment group. The trial is currently ongoing at M.D. Anderson Cancer Center. The clinical goal of the trial is to find the lowest blood level of tacrolimus that can give the highest amount of protection against GVHD with the fewest side effects possible. The randomization scheme dynamically balances the 2 arms with respect to patient age (< 45 v. ≥ 45 years) and source of cells (bone marrow vs peripheral blood). A Bayesian probability model accounting for patient prognostic covariates (age and cell source) and the times to acute GVHD, disease recurrence, and death from time of transplantation was used as a basis for constructing multiple interim monitoring rules to terminate either treatment arm for safety or stop the trial due to either futility or superiority. The rules are applied continuously throughout the trial, with either arm stopped early if the probability of acute GVHD within 100 days or disease recurrence or death within 180 days is unacceptably high. Additionally, the trial will be stopped early if the posterior probability that one arm is superior to the other in terms of their 180-day success rates exceeds 99.5%. The computer code for randomization, probability calculations (numerical integration) and simulation of the design is written in the C++ programming language using the C++ numerical library developed by the software development team in the Department of Biostatistics and Applied Mathematics at M.D. Anderson Cancer Center. The trial is being conducted using a web-based user interface with SQL server for data storage.

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DATA CONNECTION: WWW.DATAMANAGER.BLOGSPOT.COM. A CLINICAL RESEARCH PROFESSIONALS AND DATA MANAGER NETWORK

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Background. To minimize, mediate, and operate between clinical research professionals (CRPs) and data managers (DMs positioned around the world and international registries such as the CIBMTR (Center for International Blood and Marrow Transplant Research), a CRP and DM network was founded in cooperation with the CIBMTR. The aim of the network is to ensure that individual BMT centers' standard operating procedures (SOP) meet the registries' criteria in relation to documentation, data collection, and fulfillment of international requirements. To fulfill this aim, a website was launched in September 2003 including the following internal websites: "Data Connection," "News and Information," "Question and Answers," "Mentors," and "Helping Hand Guide to Data Managers" and links to external websites. These websites all address core information and communication between CRP/DMs and the CIBMTR in relation to filling out different forms, but do not address the aspects of the CRP and DM work that cross between the different registries and institutions. The aim of this study was to determine how we can help CRPs and DMs organize the daily work. **Methods.** Gather information and experiences from CRPs and DMs on how to solve these tasks and publish it on internal websites so others can benefit from their experience. **Results.** Because CRPs and DMs face audits from different registries, an audit website has been launched with experiences, tips, and ideas that might be beneficial when challenged with an audit. The internal website "Organizing the Work" conveys tips and ideas on how to organize the daily work, gather the information and source documentation required to meet the different registries as well as each institution's SOP. The aim of the "Meeting" website is to inform CRPs and DMs on upcoming meetings and important events. "Notice Board" is a website that gives CRPs and DMs an opportunity to place a notice or request. **Conclusions.** The mentoring network is a new form of IT-based cooperation and communication between CRPs, DMs, and the CIBMTR. The aim of the network and Web site is to convey news and information to provide a useful reference tool for CRPs and DMs in their daily work and to provide CRPs and DMs with a sense of belonging by filling the gap between the single BMT unit and the national/international registry. To achieve this aim, the network continues to need the support and the cooperation from CRPs, DMs, and the CIBMTR.

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IMPACT OF INFECTIOUS COMPLICATIONS ON THE OUTCOME IN PATIENTS WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background. This study was conducted to investigate the affect of infectious complications on outcome in patients with hematopoietic stem cell transplantation (HSCT). **Methods.** All patients who underwent HSCT from February 1996 to October 2003 were enrolled. Their medical records and microbiologic data were reviewed. **Results:** A total of 272 patients (136 allogenic, 133 autologous, and 3 cord HSCT) were enrolled (mean age, 37 years; mean follow-up duration, 26 months). Acute myeologeneous leukemia (27.5%) was the most common underlying disease, followed by lymphoma (19.5%) and chronic myelogeneous leukemia (14.3%). A total of 821 infectious episodes were observed in 247 patients. Infectious complications occurred more commonly in allogeneic recipients (3.57 ± 2.81 episodes) than in autologous recipients (2.62 ± 2.42 episodes) ($P = .003$). Microbiologically documented infection (MDI), clinically documented infection, and unknown fever accounted for 39.4%, 35.8%, and 24.8% of these episodes, respectively. Pneumonia (20.4%) was the most common infection, followed by primary bacteremia (13.8%) and enterocolitis (13.6%). Among 323 MDIs, bacterial infection, viral infection, and fungal infection accounted for 52.6%, 41.4%, and 6.0%, respectively. *Escherichia coli* (14.5%) was the most common bacterial isolate from blood, followed by *Klebsiella* spp. (9.8%) and *Pseudomonas* spp. (8.3%). Infectious complications developed most frequently in the early posttransplantation period (41.5%), followed by the late period (35.8%) and the intermediate period (22.7%). In the intermediate period, there were 52.2% (12/23) cases of CMV disease and 69.2% (45/65) cases of CMV infection. Relapse rate of the underlying disease was 29.4%. A total of 56 of the 74 deaths related to infection occurred in the late posttransplantation period, and 82.1% of them were related to relapse of the underlying disease. Bacteremia ($P = .004$), Gram-positive bacterial infections ($P = .028$), Gram-negative bacterial infections ($P = .043$), fungemia ($P = .02$), and fungal pneumonia ($P = .029$) were related to the mortality. **Conclusions.** Infections contributed to 60.66% of total mortality in patients with HSCT. In the late posttransplantation period, high infection-attributable mortality rate was related mainly to relapse of the underlying disease. A high rate of CMV