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Is Palivizumab Effective in the Prevention of RSV-Induced Morbidity/Mortality in Immunosuppressed Children After BMT?

The use of bone marrow transplantation (BMT) as a curative therapy for childhood malignant and nonmalignant disorders typically leads to immunosuppression, and predisposes the patient to opportunistic infections by various microbial pathogens. A major cause of morbidity and mortality among patients who have received allogeneic BMT are complications due to respiratory infection. Respiratory syncytial virus (RSV) has been identified in more than 25% of patients with documented pulmonary complications following BMT. Palivizumab, a monoclonal antibody against RSV, is a safe and effective therapeutic for prophylaxis of pediatric patients at high risk for RSV infection. However, there is a paucity of evidence for the efficacy of palivizumab in preventing RSV-associated morbidity and mortality in immunosuppressed children following BMT. Given the lack of data from randomized, double-blind, controlled studies, Thomas and colleagues utilized decision-analysis methodology to further investigate the efficacy of palivizumab in this patient population.

The investigators designed a decision tree to determine mortality from RSV-related lung disease in children who received palivizumab after transplant. Decision trees are representations of clinical decision problems that identify the relevant outcomes of a decision made by the clinician. Additional branch points from the initial decision are added and, once all the branches are completed, the tree is solved mathematically by computing the expected values of the treatment decisions. Based on these values, the decision path that leads to the most favorable outcome can be identified. In the study by Thomas et al, the subject is a pediatric patient who has undergone transplantation within the previous year and is approaching the winter season and the associated high prevalence of RSV. The initial decision branches are based on whether the patient receives palivizumab treatment throughout the winter months or not. Within their model, the investigators assumed the following: 1) the effectiveness of palivizumab is unchanged in BMT patients in comparison with other high-risk populations; 2) the rate of RSV exposure was not different in the study group when compared with the general population; 3) the criteria for hospitalization would be the same independent of receiving palivizumab; and 4) that children who were never hospitalized would not experience an RSV-related death.

Using these assumptions and information gleaned from the available literature, the base model used in this study suggested a 10% increase in survival for BMT patients treated with palivizumab. The absolute survival rate increased from 83% to 92%, suggesting that a practitioner would need to treat 12 patients to save 1 post-BMT patient from dying of RSV-related lung disease. Sensitivity analysis also demonstrated the improvement in mortality was robust over the range of biologically plausible values.

The authors conclude that in the absence of randomized, controlled, blinded studies, decision-tree modeling is a viable method to evaluate preferred outcomes. Based on the findings of this study, and the data from animal studies and phase I trials, the authors suggest that clinicians should consider the use of palivizumab in post-BMT patients until results from well-designed controlled studies are available.

Thomas NJ et al. Palivizumab prophylaxis to prevent respiratory syncytial virus mortality after pediatric bone marrow transplantation: a decision analysis model. *J Pediatr Hematol Oncol*. 2007;29:227-232.

Continued

Disclosures:
* Dr Piedra is professor of pediatrics and molecular virology and microbiology at Baylor College of Medicine. He has indicated relevant financial relationships as noted: he receives grant/research support from MedImmune, Inc. and Sanofi Pasteur; he is a member of the speakers bureau for MedImmune, Inc.; he is an expert witness for Sanofi Pasteur; he is an ad hoc consultant for MedImmune, Inc., Sanofi Pasteur, GlaxoSmith-Kline, Novartis, and Roche; and he is part of a collaborative research agreement with NIH and Baylor.
† Dr Welliver is professor of pediatrics at the State University of New York at Buffalo. He has indicated relevant financial relationships as noted: he is a member of the speakers bureau for MedImmune, Inc., is an ad hoc consultant for Cubist, Inc. and MedImmune, Inc.; and receives clinical trials support from MedImmune, Inc.
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prci Pediatric Respiratory Care Initiative™

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Learning Objectives
After studying the literature presented in this issue, participants will be able to

- Describe the impact of palivizumab treatment on survival of post–bone marrow transplant, pediatric patients
- Assess the tolerability, toxicity, and therapeutic potential of prophylaxis with oseltamivir for influenza infection in hematopoietic stem cell transplantation recipients

Target Audience
This educational activity is designed for pediatricians, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other healthcare professionals involved in the care and management of pediatric respiratory patients.

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What is more clear from the data are that oseltamavir appeared to be reasonably well tolerated, did not contribute to adverse events, and that prophylaxis was important in managing and aborting an outbreak of influenza in a high-risk population.

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COMMENTARY

ROBERT C. WELLIVER, MD, Professor of Pediatrics, State University of New York at Buffalo, Women and Children's Hospital, Buffalo, New York.

Respiratory syncytial virus (RSV) is best known as the major cause of bronchiolitis in infancy. Nevertheless, its role in pneumonia in the elderly and in immunocompromised patients is now becoming recognized. Initial reports described high mortality rates from RSV infection in those undergoing bone marrow transplantation. In this study, Thomas and colleagues undertake a commendable effort to determine the efficacy of palivizumab (a monoclonal antibody against the fusion protein of RSV) among such patients.

Such studies are important, given the extremely high cost of administration of palivizumab to adults (ie,15 mg/kg of body weight), but they are difficult to carry out. In this case, a decision-tree analysis was performed in lieu of a controlled study. This requires the acceptance of risk estimates for which confirmatory data are often unavailable. Selecting a 20% risk of exposure to RSV for these subjects seems appropriate, but there is almost no basis for determining how many of these subjects will develop RSV pneumonia upon exposure. This is because there are far more asymptomatic (undetected) infections in older children and adults than in infants, from whom the estimates used were derived. The authors are correct in assuming a high rate of hospitalization for pneumonia cases, but their chosen mortality rate of 69% is high based on results of several recent studies.

I agree with the conclusion that palivizumab prophylaxis should be considered strongly in order to prevent RSV infection in these subjects. Nevertheless, there is a great need for harder data regarding efficacy (and some comment on the cost) of palivizumab in this setting before final recommendations can be put forth.

Oseltamivir for Treatment Against Nosocomial or Community Influenza in HSCT Patients

Individuals receiving hematopoietic stem cell transplantation (HSCT) are at high risk of developing complications of influenza infection because of their immunocompromised status. Community-acquired respiratory virus infections in this population are associated with transplant-related mortality and thus pose a serious health risk. In fact, among HSCT patients with influenza pneumonia, the 30-day mortality rate can be as high as 28%.

The neuraminidase inhibitor oseltamivir is a safe and effective treatment for influenza. However, there are no rigorous clinical trial data to support the use of oseltamivir for prophylactic treatment against nosocomial or community influenza infections in HSCT patients. Using data from a 2002 outbreak of influenza A in a housing facility for HSCT candidates and those receiving HSCT-related outpatient care, Vu et al performed a retrospective study to determine the oseltamivir-associated toxicities in this population.

Oseltamivir prophylaxis (75 mg/day) was initiated for asymptomatic patients living in the housing facility upon recognition of the onset of the outbreak. Study subjects received oseltamivir for a median of 17 days (range: 10-81 days). Chart data obtained for 25 post-HSCT patients and 20 HSCT candidates who received oseltamivir prophylaxis was retrospectively analyzed for adverse events. These patients were matched 1:1 with control subjects who received transplants from 1994-2003 and who did not receive prophylactic treatment. Patient matching was done based on donor type, conditioning regimen, cytomegalovirus serostatus, time after HSCT, and recipient age (± 5 years).

Following prophylaxis, no new cases of influenza were identified. However, 7 weeks postinitiation of prophylaxis, 1 subject with a documented record of noncompliance did develop an influenza B infection, which resolved with oseltamivir therapy. Similarly, a single influenza B infection was reported for a subject who did not receive prophylaxis. This patient tested positive for cytomegalovirus and, despite therapy with oseltamivir and ganciclovir, subsequently died of respiratory failure. No deaths attributable to prophylaxis occurred. Evaluation of 11 clinical adverse events, including nausea, vomiting, fatigue, abdominal pain, and diarrhea revealed no difference between the case subjects and the control group.

The authors suggest that, although the efficacy of prophylaxis are difficult to evaluate because the study was not being done in a prospective, randomized fashion, it is interesting to note that the outbreak was immediately aborted. What is more clear from the data are that oseltamivir appeared to be reasonably well tolerated, did not contribute to adverse events, and that prophylaxis was important in managing and aborting an outbreak of influenza in a high-risk population. Furthermore, while prophylaxis with oseltamivir is not part of current guidelines for chemoprophylaxis in HSCT recipients, the authors suggest that it be considered as a preventive option during influenza outbreaks.

Vu D et al. Safety and tolerability of oseltamivir prophylaxis in hematopoietic stem cell transplant recipients: a retrospective case-control study. *Clin Infect Dis*. 2007;45:187-193.

Clinical Insights® in Pediatric Respiratory Care Post-Test

1. According to the findings reported by Thomas et al, how many post-BMT patients would a practitioner need to treat with palivizumab to save 1 from dying of RSV-associated lung disease?
   a. 9
   b. 10
   c. 11
   d. 12

2. When comparing patients who received oseltamivir prophylaxis during an influenza outbreak with a control group that did not receive oseltamivir, how did the prophylactic treatment affect clinical adverse events?
   a. Oseltamivir prophylaxis caused a significant increase in clinical adverse events
   b. Oseltamivir prophylaxis reduced the number of clinical adverse events
   c. There was no difference between the study and control groups
   d. Oseltamivir treatment did not alter clinical adverse events but did result in more deaths

1. *d.* A practitioner would need to treat 12 patients to save 1 post-BMT patient from dying of RSV-related lung disease.
2. *c.* Evaluation of 11 clinical adverse events, including nausea, vomiting, fatigue, abdominal pain, and diarrhea revealed no difference between the case subjects and the control group.

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Overall Program

	Strongly Disagree		Disagree	Agree		Strongly Agree
1. The activity met the stated objectives in such a way that I am better able to:						
a. Describe the impact of palivizumab treatment on survival of post–bone marrow transplant, pediatric patients	1	2	3	4	5	6
b. Assess the tolerability, toxicity, and therapeutic potential of prophylaxis with oseltamivir for influenza infection in hematopoietic stem cell transplantation recipients	1	2	3	4	5	6

2. Overall, the activity was presented in a fair-balanced manner. ☐ Yes ☐ No*
   * If you checked "No," please explain. _____

3. Overall, the activity was free of commercial bias. ☐ Yes ☐ No*
   * If you checked "No," please explain. _____

4. In reflecting on your practice, what type of impact will this educational activity have?
   ☐ Consider prophylaxis with palivizumab to potentially protect BMT recipients against RSV-related lung disease and its associated morbidity and mortality
   ☐ Recognize that prophylactic treatment of HSCT recipients with oseltamivir may be important in managing an outbreak of influenza in a high-risk population

   I will:
   ☐ Consider prophylactic treatment with oseltamivir or palivizumab in transplant patients
   ☐ Be able to better describe the potential of prophylactic antiviral treatment to my patients

5. What topics should be dealt with in more detail? (*List topics.*)
   _____ _____
   _____ _____

Thank you for your participation.