conception and design, data analysis, and manuscript review and final approval.

REFERENCES

1. Gebel HM, Bray RA. Approaches for transplanting the sensitized patient: biology versus pharmacology. *Nephrol Dial Transplant*. 2008;23:2454-2457.
2. Ciurea SO, de Lima M, Cano P, et al. High risk of graft failure in patients with anti-HLA antibodies undergoing haploidentical stem cell transplantation. *Transplantation*. 2009;88:1019-1024.
3. Spellman S, Bray R, Rosen-Bronson S, et al. The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. *Blood*. 2010;115:2704-2708.
4. Takanashi M, Atsuta Y, Fujiwara K, et al. The impact of anti-HLA antibodies on unrelated cord blood transplantations. *Blood*. 2010;116:2839-2846.
5. Takanashi M, Fujiwara K, Tanaka H, et al. The impact of HLA antibodies on engraftment of unrelated cord blood transplants. *Transfusion*. 2008;48:791-793.
6. Brunstein CG, Barker JN, Weisdorf DJ, et al. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. *Blood*. 2007;110:3064-3070.
7. Brunstein CG, Gutman JA, Weisdorf DJ, et al. Allogeneic hematopoietic cell transplantation for hematological malignancy: relative risks and benefits of double umbilical cord blood. *Blood*. 2010;116:4693-4699.
8. Ramirez P, Wagner JE, DeFor TE, et al. The kinetics of chimerism and factors that predict single unit predominance after double umbilical cord blood transplantation. *Blood*. 2010;116:105.
9. Lin DY. Non-parametric inference for cumulative incidence functions in competing risks studies. *Stat Med*. 1997;16:901-910.
10. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.
11. Gutman JA, McKinney SK, Pereira S, et al. Prospective monitoring for alloimmunization in cord blood transplantation: "virtual crossmatch" can be used to demonstrate donor-directed antibodies. *Transplantation*. 2009;87:415-418.

Safety and Immunogenicity of the Live Attenuated Varicella Vaccine Following T Replete or T Cell-Depleted Related and Unrelated Allogeneic Hematopoietic Cell Transplantation (alloHCT)

Joanne F. Chou, Nancy A. Kernan, Susan Prockop, Glenn Heller, Andromachi Scaradavou, Rachel Kobos, Molly A. Knowles, Esperanza B. Papadopoulos, Anne Casson, Catherine Copeland, Joanne Torok-Castanza, Nicole Zakak, Julianne Ruggiero, Trudy N. Small

There are limited studies assessing the live attenuated varicella vaccine following allogeneic hematopoietic cell transplantation (alloHCT). Because of the morbidity of varicella acquired after childhood, we immunized and retrospectively analyzed the safety and immunogenicity of this vaccine in 46 varicella zoster virus (VZV) seronegative patients <20 years old at HCT who achieved a CD4 cell count ≥200/μL, were off immunosuppression, and responded to ≥1 post-HCT vaccines. Two vaccinated patients lacking follow-up titers were excluded from analysis. Stem cells were derived from an HLA-matched sibling (n = 18) or an alternative (HLA mismatched related or unrelated) donor (n = 26). Median time to vaccination was 4 years. Sixty-four percent of patients seroconverted following 1 immunization. There was no significant difference in response between recipients of a matched related or alternative donor graft ($P = .2$) or between those given a T cell-depleted or T-replete alternative donor graft ($P = .27$). Three of 44 patients developed a self-limited varicella-like rash within 2.5 weeks of immunization. With a median follow-up of 29.1 (range: 6.9-167.1) months, there were no subsequent cases of varicella-like rashes. No patient developed shingles. This study

From the Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York City, New York.
Financial disclosure: See Acknowledgments on page 1712.
Correspondence and reprint requests: Trudy N. Small, MD, Department of Pediatrics, Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065 (e-mail: smallt@mskcc.org).
Received April 12, 2011; accepted May 5, 2011

1083-8791/$36.00
doi:10.1016/j.bbmt.2011.05.006

suggests that this vaccine is safe and immunogenic when given according to preset clinical and immunologic milestones, warranting larger prospective studies in patients ≥24 months following HCT as outlined in current post-HCT vaccine guidelines.

Biol Blood Marrow Transplant 17: 1708-1713 (2011) © *2011 American Society for Blood and Marrow Transplantation*

KEY WORDS: Varicella, Allogeneic, Immunization

INTRODUCTION

Although varicella in childhood is generally a mild disease, immunocompetent individuals who develop chickenpox later in life develop a more serious infection, associated with an increased risk of visceral disease and need for hospitalization [1,2]. In individuals >20 years of age, fatal varicella is 13 times higher than that observed in children [2]. Studies have documented the safety and efficacy of the live attenuated varicella vaccine in healthy children [3] and patients with a history of impaired cellular or humoral immunity [4,5], such as children with acute lymphoblastic leukemia on maintenance therapy [6], pediatric solid organ transplant recipients on chronic immunosuppressive therapy [7,8], and treated children with HIV [9-11]. In view of this, our center has chosen to vaccinate varicella zoster virus (VZV) seronegative children and adolescents after allogeneic hematopoietic cell transplantation (alloHCT) upon acquisition of preset immune milestones. Although both the 2005 European Group for Blood and Marrow Transplantation (EBMT) [12] and the 2009 [13] Center for International Blood and Marrow Transplant Research (CIBMTR) vaccine guidelines permit the use of a live attenuated varicella vaccine in select patient groups, there is minimal data on the immunogenicity of this vaccine post-HCT [14-16], particularly in recipients of cord blood, unrelated HCT derived from any source, and children transplanted for primary immunodeficiency disease. In view of this, this retrospective study analyzed the safety and immunogenicity of this vaccine in allogeneic transplantation recipients. The effect of age at transplantation and vaccination, diagnosis, time from HCT to vaccination, donor type, and stem cell source, history of graft-versus-host disease (GVHD), and/or the use of T cell depletion on vaccine responses was assessed.

PATIENTS, MATERIALS, AND METHODS

A waiver of authorization to conduct this study was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) institutional review board. The medical records of all patients <20 years old at HCT who were disease-free for >10 months following an allogeneic transplantation performed from 1/1/1995 through 12/1/08 were reviewed for receipt of the live attenuated varicella vaccine. At this center, VZV seronegative patients were eligible for vaccination if they were ≥24 months following transplantation, were off all immunosuppressive therapy, and had no evidence of ongoing chronic GVHD (cGVHD). To increase vaccine safety, patients were required to have a circulating CD4 cell count (>200 cells/μL), a T cell proliferative response against Phytohemagglutinin (PHA) within the lower limit of normal, and a specific antibody response to ≥1 vaccines administered post-HCT. Four patients were immunized by their local physicians <2 years post-HCT despite our recommendations to delay immunization until ≥24 months. Dates of vaccination and pre- and postvaccine titers were obtained from a prospectively maintained database and confirmed by retrospective chart review. Pre- and posttiters were available on 44 patients; 2 vaccinated patients without follow-up titers were excluded from analysis. All patients were evaluated at MSKCC before and after completing vaccinations, including assessment of acute (aGVHD) and cGVHD using established criteria [17,18]. Ninety percent of patients were vaccinated at MSKCC.

Immunologic Evaluations

Antibody testing

Varicella antibody was measured in the Clinical Microbiology Laboratory of MSKCC using a 2-step enzyme immunoassay sandwich method with a final fluorescent detection (BIOMERIEUX, Durham, NC). The result is indicated by test value calculated by the computer based on the ratio from the relative fluorescent value of the sample to that of the standards that are run for each test. A test value >0.9 is considered positive.

Four-color immunofluorescence and T cell proliferative responses

Circulating lymphoid populations were analyzed by 4-color immunofluorescence within 3 months of initiating vaccination using methods as previously described [19]. In vitro T cell proliferative responses to phytohemagglutinin and varicella virus were performed as follows: 50,000 isolated peripheral blood mononuclear cells were resuspended in RPMI, supplemented with 10% pooled human serum, penicillin/streptomycin, and L-glutamine, and plated in round-bottom microtiter wells in a volume of 175 μL/well. Cells were stimulated with phytohemagglutinin (PHA-P, DIFCO, Sparks, MD) at optimal final concentrations of 42.9, 21.4, and 10.7 μg/mL of culture and Varicella Zoster CF antigen (1:10, 1:20, 1:40, 1:80 dilution)

Table 1. Patient and Donor Characteristics

	N = 44
Age (range) at HCT	4.5 (0.1-19) years
Sex (male/female)	25/19
Diagnosis:	
Hematologic malignancy	25
Immunodeficiency (SCID/WAS)	10 (7/3)
Other:	9
Hemoglobinopathy	4
Hemophagocytic lymphohistiocytosis	2
Kostman's syndrome	1
Wolman's syndrome	1
Aplastic anemia	1
Time (median, range) from HCT to vaccine	4.0 (0.92-14.04) years
Age (range) at vaccination	8.9 (2.48-31.3) years
Transplant type	
Unmodified (n = 31)	
HLA-Matched sibling	17
Unrelated Adult donor	8
Unrelated cord blood (single/double unit)	5 (1/4)
T cell depleted (n = 13)	
HLA Matched sibling	1
HLA Mismatched Related	6
Unrelated	7

HCT indicates hematopoietic cell transplantation; SCID, severe combined immunodeficiency.

(BioWhittaker, Walkersville, MD). Cultures were pulse labeled with 1.0 μCi/well ^{3}H-thymidine for the last 24 hours of the 120-hour incubation for PHA and 168 hours for varicella, harvested onto glass-fiber filter paper, and counted in a liquid scintillation counter. The absolute proliferative response was calculated as the median counts per minute (cpm) of triplicate wells minus the unstimulated medium control. Each day, all assays performed on patients were run in parallel with a normal control and compared with values derived from 60 normal controls evaluated every 2 years.

Statistical Analysis

The Fisher exact test and the Wilcoxon rank sum test was used to examine covariate differences between responders and nonresponders. The SAS statistical package (version 9.2) (SAS Institute Inc., Cary, NC) was used to generate the test statistics. Only P values $<.05$ were considered statistically significant.

Patient and Transplant Characteristics

Patient and donor characteristics are shown in Table 1. The majority of patients were transplanted for a hematologic malignancy (57%) or primary immunodeficiency disease (23%). The stem cell donor was an HLA-A, B, DRβ1 identical sibling, a haplo-identical family member, or an unrelated donor in 41%, 14%, and 45% of cases, respectively. Seventy percent of patients received an unmodified HCT. Of the remaining 13 patients, 8 received a bone marrow transplant (BMT) T cell depleted by either soybean lectin agglutination followed by rosetting with sheep erythrocytes (n = 6) [20] or treatment with the T10B9 monoclonal antibody plus complement (n = 2) [21], and 5 received a peripheral blood stem cell graft T cell depleted by CD34 positive selection followed by rosetting with sheep erythrocytes [22]. Eight-nine percent of patients received myeloablative cytoreduction that contained either hyperfractionated total body irradiation (TBI) (n = 15) or >8 mg/kg busulfan (n = 24). Three patients received nonmyeloablative conditioning (melphalan, fludarabine, anti-CD52 [n = 2] or cyclophosphamide, and antithymocyte globulin [ATG; n = 1]). Two patients with severe combined immunodeficiency disease (SCID) received an HLA matched sibling BMT without prior cytoreduction. Three patients received posttransplantation rituximab at 25, 49, and 50 months before vaccination for the treatment of a severe autoimmune hemolytic anemia following an unmodified, unrelated BMT (n = 1) or to prevent an Epstein-Barr virus lymphoproliferative disorder following a T cell-depleted unrelated peripheral blood stem cell transplantation (n = 2). Six patients had a history of grade II-III aGVHD, and 3 patients developed cGVHD, which had resolved in all patients before vaccination.

RESULTS

Before receipt of the live attenuated varicella vaccine, all patients were VZV seronegative, and 42 of 44 patients lacked a T cell proliferative response against varicella antigen. The median age at vaccination was 9 years. The median time from transplantation to vaccination was 4 years, with a range of 0.92-14.04 years. The wide range between HCT and immunization was because of the time it took patients to discontinue immunosuppression, reach immunologic milestones, and/or physician comfort administering the live attenuated varicella vaccine. There was no significant difference in time to vaccine in recipients of T cell-depleted or T-replete transplantation. The median time to first live attenuated varicella vaccine was 3.9 (range: 0.92-14.04) years following a T cell-depleted HCT and 4.1 (range: 1.67-9.13) years postunmodified HCT, $P = .64$.

B and T Cell-Specific Responses

The median time to measure antibody levels following the initial vaccine was 108 days (range: 29-395 days). Overall, 64% (28 of 44) of patients seroconverted following 1 vaccine. There was no significant difference in the proportion of responders in patients evaluated < or >108 days postimmunization (14 of 23 vs 15 of 22). Response was observed in 50% (7 of 14), 68% (13 of 19), and 73% (8 of 11) of patients immunized between 0.92 and 3, 3 and 5, and >5 years post-HCT. There was no significant difference in B cell response on the basis of age at HCT, age at vaccination, patient diagnosis, or history of resolved aGVHD or cGVHD (data not shown). Eight of 10 patients transplanted for a primary

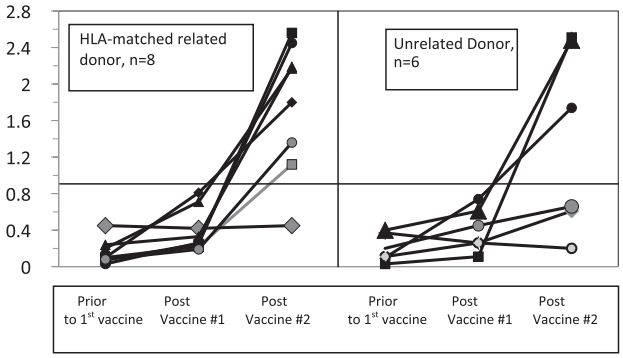

Figure 1. Antibody response following second live attenuated varicella vaccine in patients who did not seroconvert following their initial vaccine (n = 14). This figure demonstrates VZV titers in 14 patients given a second varicella vaccine following lack of response to initial immunization. The figure demonstrates VZV titer obtained before the vaccine (pretiter), following the first immunization, and again following the second immunization. Response is shown in 8 recipients of an HLA-matched sibling HCT (left) and 6 recipients of an unrelated HCT (right). Horizontal line drawn at value of 0.9, above which is positive.

immunodeficiency disease responded to the first live attenuated varicella vaccine administered at a median (range) of 3.3 (1.6-4.9) years post-HCT. There was no significant difference in response in recipients of an HLA matched related compared with an alternative donor HCT (9 of 18 vs 19 of 26), respectively ($P = .2$). Ten of 12 and 9 of 14 recipients of a T cell-depleted or T-replete alternative donor HCT seroconverted after 1 live attenuated varicella vaccine, respectively ($P = .27$). Three of 5 patients who received a cord blood transplant seroconverted following their first vaccine administered at a median (range) of 3.76 (2.76-5.89) months post-HCT.

Fourteen patients who did not respond to the first live attenuated varicella vaccine received a second immunization at a median of 7.2 (range: 2.7-14.6) months following the primary live attenuated varicella vaccine. Seven of 8 recipients of an unmodified HLA matched sibling HCT and 3 of 6 recipients of an unrelated HCT ($P = .16$) seroconverted following the second vaccine (Figure 1).

Following the initial live attenuated varicella vaccine, in vitro T cell proliferative response against VZV was assessed in 17 patients who seroconverted and 14 patients who did not. Of the 17 patients who mounted a B cell response, 13 developed a VZV specific T cell proliferative response. Despite failure to seroconvert, 7 of 14 patients developed a specific in vitro T cell response against varicella.

Safety

No patient suffered a serious adverse reaction attributable to vaccination. Three unrelated transplant recipients (cord blood, n = 1; unmodified PBSCT, n = 1; T10B9 + complement TCD BMT, n = 1), developed a mild (<25 vesicles) disseminated rash within 2.5 weeks of vaccination. The rash resolved in all 3 patients within 7 days of onset without treatment. Currently, 43 of 44 patients are alive, disease-free with a median (range) follow-up of 29.1 (6.9-167.1) months postimmunization. There have been no cases of primary varicella or a varicella-like rash >2.5 weeks postvaccination nor any cases of shingles. No patient has required acyclovir, gammaglobulin, or hyperimmune zoster immune globulin since vaccination.

DISCUSSION

Reactivation of wild-type varicella is known to cause significant morbidity and occasionally mortality following an alloHCT [23,24]. The risk of shingles in younger patients whose VZV immunity was acquired through vaccination rather than wild-type disease is currently unknown. In addition, patients immunized in early childhood who undergo HCT later in life may be at an increased risk of varicella because of the known loss of vaccine immunity even in healthy recipients of a single live attenuated varicella vaccine [25]. In a 10-year study by Chaves et al. [26] of 11,356 healthy vaccinated subjects, 1080 developed breakthrough varicella. The annual rate of breakthrough disease increased significantly with time following immunization, with 1.6 compared with 58.2 cases per 1000 person-years occurring within 1 year and 9 years post-live attenuated varicella vaccine, respectively. The risk of breakthough disease was highest in children 8 to 12 years of age who were 5 or more years following immunization.

Although both the 2005 EBMT [12] and 2009 CIBMTR [13] guidelines permit the use of the live varicella vaccine in select patient groups starting at 24 months post-HCT, only 2 published studies have assessed safety and/or response in alloHCT recipients. Sauerbrei and colleagues [14] vaccinated 15 pediatric patients, 8 of whom received an alloHCT. Patients were vaccinated at a median of 18 (range: 12-23) months post-HCT. Immunologic criteria for vaccination included a circulating lymphocyte count of >1000 cells/μL, serum IgG >500 mg/dL, and a positive skin test to a recall antigen. Of the 4 VZV seronegative allogeneic patients immunized, 3 of 4 seroconverted at 6 weeks postimmunization. Kussmaul and colleagues [15] evaluated the safety of the live attenuated varicella vaccine in 18 autologous and 50 alloHCT recipients, 25 of whom were evaluable for response. Eligibility for vaccination included a circulating CD4 count of ≥200 cells/μL, a PHA response at least 50% of the lower limit of normal, a humoral response to the inactivated polio vaccine, and specific T and B cell response to tetanus toxoid. The median time to the first live attenuated varicella vaccine was 32 months post-HCT (range: 16-144 months). There were no serious vaccine-related events. Although the study by Kussmaul et al. [16] did not stipulate the proportion of responders who received an autologous versus an alloHCT, of the

25 patients clearly evaluable for response, seroconversion occurred in 40%, 8%, and 4% of patients after 1, 2, or 3 vaccines, respectively.

Our study, although retrospective, represents the largest series analyzing the response of VZV seronegative patients following HCT vaccinated with live attenuated varicella vaccine. Although an ELISA was used to assess response, the seroconversion rate following the live attenuated varicella vaccine in our study is not markedly different than the 74% conversion rate observed in healthy children when measured by the highly sensitive fluorescent antibody to membrane antigen (FAMA) [27]. The latter assay requires viral propagation in tissue culture, is not commercially available, and requires considerable operator expertise. In view of this, several studies [7-9,14,16], including ours, have used an ELISA-based method to measure response to the live attenuated varicella vaccine.

The risk of shingles following the live attenuated varicella vaccine has been 1 of the main concerns surrounding immunization of children against chickenpox, particularly those with a history of or ongoing immunodeficiency [27,28]. This risk has been evaluated in children with a history of leukemia [29], pediatric recipients of solid organ transplants [7,8], and HIV infected children on retroviral therapy [9-11]. Studies in these populations have not shown an increased risk of VZV. In 1989, Lawrence et al. [28] compared the risk of shingles in children with acute lymphoblastic leukemia (ALL) in remission who were immunized versus those with a history of natural infection. Of the 346 immunized children, the incidence of zoster was 0.552 cases/100 person-years. In a subset of 82 matched pairs, there was no significant difference in the incidence of shingles in patients who were vaccinated (1.23 cases per 100 person-years) compared with 3.11 cases in children with a history of varicella, respectively (P = NS). In 2009, Civen and colleagues [29] demonstrated that immunized children <10 years old had a 4 to 12 times lower risk of developing shingles than children with a history of chickenpox.

Because of breakthrough cases of varicella in recipients of a single vaccine, the Advisory Committee on Immunization Practices (ACIP) currently recommends a 2-dose schedule in healthy children at 12 to 15 months and 4 to 6 years, a second dose in children, adolescents, and adults previously given only 1 vaccine, routine immunization of all healthy VZV seronegative individuals 13 years of age or older, and immunization of HIV-infected children and adults with circulating $CD4^+$ T lymphocyte counts >200 cells/μL [3]. Our study supports the use of the live attenuated varicella vaccine in VZV seronegative patients. The dichotomy of T and B cell responses in some of our patients (ie, seroconversion in the absence of concurrent T cell response) suggest that kinetics of recovery of lymphoid populations required for a full response may differ from patient to patient. Larger prospective trials assessing the safety, immunogenicity, protection against chickenpox, and subsequent risk of shingles following the live attenuated varicella vaccine in this population are needed. Ideally, trials should be designed to identify biological markers that might allow earlier revaccination of patients with the requisite T and B cell populations and prevent premature vaccination and/or risk in patients unable to respond.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported by CA23766 (T.N.S.) and the National Shingles Foundation (T.N.S.).

AUTHORSHIP STATEMENT

T.N.S. designed the study and wrote the manuscript with the help of J.F.C., N.A.K., S.P., E.B.P., A.S., and R.K. J.F.C., T.N.S., and G.H. performed the biostatistics. T.N.S. M.A.K., A.C., C.C., J.T.-C., N.C., and J.R. collected the data.

REFERENCES

1. Arbeter AM. Clinical trials of varicella vaccine in healthy adolescents and adults. *Infect Dis Clin North Am*. 1996;10:609-615.
2. Tunbridge AJ, Breuer J, Jeffery KJ. British Infection Society. Chickenpox in adults. *J Infect*. 2008;57:95-102.
3. Marin M, Güris D, Chaves SS, Schmid S, Seward JF. Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56:1-40.
4. Galea SA, Sweet A, Beninger P, et al. The safety profile of varicella vaccine: a 10-year review. *J Infect Dis*. 2008;197(Suppl 2): S165-S169.
5. Satori AM. A review of the varicella vaccine in immunocompromised individuals. *Int J Infect Dis*. 2004;8:259-270.
6. Gershon AA, Steinberg SP, Gelb L, et al. Live attenuated varicella vaccine. Efficacy for children with leukemia in remission. *JAMA*. 1984;252:355-362.
7. Khan S, Erlichman J, Rand EB. Live virus immunization after orthotopic liver transplantation. *Pediatr Transplant*. 2006;10:78-82.
8. Weinberg A, Horslen SP, Kaufman SS, et al. Safety and immunogenicity of varicella-zoster virus vaccine in pediatric liver and intestine transplant recipients. *Am J Transplant*. 2006;6:565-568.
9. Armenian SH, Han JY, Dunaway TM, Church JA. Safety and immunogenicity of live varicella virus vaccine in children with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. 2006;25:368-370.
10. Taweesith W, Puthanakit T, Kowitdamrong E, et al. The immunogenicity and safety of live attenuated varicella-aoster virus vaccine in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2011;30:320-324.
11. Son M, Shapiro ED, LaRussa P, et al. Effectiveness of varicella vaccine in children infected with HIV. *J Infect Dis*. 2010;20: 1806-1810.
12. Ljungman P, Engelhard D, de la Cámara R, et al. Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT. *Bone Marrow Transplant*. 2005;35:737-746.

13. Ljungman P, Cordonnier C, Einsele H, et al. Vaccination of hematopoietic cell transplant recipients. *Bone Marrow Transplant*. 2009;44:521-526.
14. Sauerbrei A, Prager J, Hengst U, Zintl F, Wutzler P. Varicella vaccination in children after bone marrow transplantation. *Bone Marrow Transplant*. 1997;20:381-383.
15. Small TN, Kernan NA, Prockop S, et al. Immunogenicity of the live attenuated varicella vaccine following allogeneic HCT. *Blood*. 2009;114:468a.
16. Kussmaul SC, Horn BN, Dvorak CC, Abramovitz L, Cowan MJ, Weintrub PS. Safety of the live, attenuated varicella vaccine in pediatric recipients of hematopoietic SCTs. *Bone Marrow Transplant*. 2010;45:1602-1606.
17. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*. 1974;18: 295-304.
18. Sullivan KM, Shulman HM, Storb R, et al. Chronic graft-versus-host disease in 52 patients: adverse natural course and successful treatment with combination immunosuppression. *Blood*. 1981;57:267-276.
19. Small TN, Papadopoulos EB, Boulad F, et al. Comparison of immune reconstitution after unrelated and related T-cell depleted bone marrow transplantation: effect of patient age and donor leukocyte infusions. *Blood*. 1999;93:467-480.
20. Reisner Y, Kapoor N, Kirkpatrick D, et al. Transplantation for severe combined immunodeficiency disease with HLA-A, B, D, DR incompatible parental marrow cells fractionated by soybean agglutination and sheep red blood cells. *Blood*. 1983;61:341-348.
21. Casper J, Camitta B, Truitt R, et al. Unrelated bone marrow transplants for children with leukemia or myelodysplasia. *Blood*. 1995;85:2354-2363.
22. Jakubowski AA, Small TN, Young JW, et al. T cell depleted stem-cell transplantation for adults with hematologic malignancies: sustained engraftment of HLA-matched related donor grafts without the use of antithymocyte globulin. *Blood*. 2007; 110:4552-4559.
23. Kawasaki H, Takayama J, Ohira M. Herpes zoster infection after bone marrow transplantation in children. *J Pediatr*. 1996;128: 353-356.
24. Leung TF, Chik KW, Li CK, et al. Incidence, risk factors and outcome of varicella-zoster virus infection in children after haematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2000;25:167-172.
25. Galil K, Lee B, Strine T, et al. Outbreak of varicella at a day-care center despite vaccination. *N Engl J Med*. 2002;347:1909-1915.
26. Chaves SS, Gargiullo P, Zhang JX, et al. Loss of vaccine-induced immunity to varicella over time. *N Engl J Med*. 2007;356: 1121-1129.
27. Gershon A, Katz SL. Perspective on live varicella vaccine. *J Infect Dis*. 2008;197(Suppl 2):S242-S245.
28. Lawrence R, Gershon A, Holzman R, Steinberg SP. The risk of zoster after varicella vaccination in children with leukemia. *N Eng J Med*. 1988;18:543-548.
29. Civen R, Chaves SS, Jumaan A, et al. The incidence and clinical characteristics of herpes zoster among children and adolescents after implementation of varicella vaccination. *Pediatr Infect Dis J*. 2009;28:954-959.

The Incidence of Veno-Occlusive Disease Following Allogeneic Hematopoietic Stem Cell Transplantation Has Diminished and the Outcome Improved over the Last Decade

Enric Carreras, Marina Díaz-Beyá, Laura Rosiñol, Carmen Martínez, Francesc Fernández-Avilés, Montserrat Rovira

The evolution of the incidence, morbidity, and mortality of veno-occlusive disease (VOD) was analyzed in 845 allogeneic hematopoietic stem cell transplantations (allo-HSCTs) performed over 24 years. A total of 117 patients and 73 patients developed VOD following the Seattle and the Baltimore diagnostic criteria, respectively (cumulative incidence 13.8% and 8.8%). The cumulative incidence was significantly higher in the period 1985 to 1996 than in 1997 to 2008 (11.5% vs 6.5%; $P = .01$). This decline was because of the low incidence of VOD among reduced-intensity conditioning-HSCT (RIC-HSCT) (2.1%) and the reduction among those receiving myeloablative-HSCT from unrelated donors (32.7% vs 10.5%, $P = .001$). A total of 35 patients had severe VOD (26 with multiorgan failure [MOF]), and 20 died by VOD (cumulative mortality rate

From the BMT Unit, Hematology Department, Hospital Clinic, Institut d'Investigacions Biomèdiques Agustí Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain.

Financial disclosure: See acknowledgments on page 1719.

Correspondence and reprint requests: Enric Carreras, MD, BMT Unit, Hematology Department, Hospital Clínic, Institut d'Investigacions Biomèdiques Agustí Pi i Sunyer (IDIBAPS), University of Barcelona, Villarroel 170, 08036 Barcelona, Spain (e-mail: carreras@clinic.ub.es).

Received March 30, 2011; accepted June 14, 2011

1083-8791/$36.00
doi:10.1016/j.bbmt.2011.06.006