

Improved survival after acute graft-versus-host disease diagnosis in the modern era

Hanna J. Khoury,¹ Tao Wang,^{2,3} Michael T. Hemmer,² Daniel Couriel,⁴ Amin Alousi,⁵ Corey Cutler,⁶ Mahmoud Aljurf,⁷ Joseph H. Antin,⁶ Mouhab Ayas,⁷ Mino Battiwalla,⁸ Jean-Yves Cahn,⁹ Mitchell Cairo,¹⁰ Yi-Bin Chen,¹¹ Robert Peter Gale,¹² Shahrukh Hashmi,^{13,14} Robert J. Hayashi,¹⁵ Madan Jagasia,¹⁶ Mark Juckett,¹⁷ Rammurti T. Kamble,¹⁸ Mohamed Kharfan-Dabaja,¹⁹ Mark Litzow,¹³ Navneet Majhail,²⁰ Alan Miller,¹⁸ Taiga Nishihori,¹⁹ Muna Qayed,²¹ Helene Schoemans,²² Harry C. Schouten,²³ Gerard Socie,²⁴ Jan Storek,²⁵ Leo Verdonck,²⁶ Ravi Vij,²⁷ William A. Wood,²⁸ Lolie Yu,²⁹ Rodrigo Martino,³⁰ Matthew Carabasi,³¹ Christopher Dandoy,³² Usama Gergis,³³ Peiman Hematti,¹⁷ Melham Solh,³⁴ Kareem Jamani,²⁵ Leslie Lehmann,³⁵ Bipin Savani,¹⁶ Kirk R. Schultz,³⁶ Baldeep M. Wirk,³⁷ Stephen Spellman,³⁸ Mukta Arora³⁹ and Joseph Pidala¹⁹

¹Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA; ²CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; ³Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI, USA; ⁴Utah Blood and Marrow Transplant Program-Adults, Salt Lake City, UT, USA; ⁵Department of Stem Cell Transplantation, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ⁶Center for Hematologic Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; ⁷Department of Pediatric Hematology Oncology, King Faisal Specialist Hospital Center & Research, Riyadh, Saudi Arabia; ⁸Hematology Branch, National Heart, Lung and Blood Institute-NIH, Bethesda, MD, USA; ⁹Department of Hematology, University Hospital, Grenoble, France; ¹⁰Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Department of Pediatrics, New York Medical College, Valhalla, NY, USA; ¹¹Division of Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA; ¹²Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, UK; ¹³Department of Internal Medicine, Mayo Clinic Rochester, MN, USA; ¹⁴Department of Oncology, King Faisal Specialist Hospital Center & Research, Riyadh, Saudi Arabia; ¹⁵Division of Pediatric Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine in St. Louis, MO, USA; ¹⁶Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN, USA; ¹⁷Division of Hematology/Oncology/Bone Marrow Transplantation, Department of Medicine, University of Wisconsin Hospital and Clinics, Madison, WI, USA; ¹⁸Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX, USA; ¹⁹Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; ²⁰Blood & Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; ²¹Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA; ²²University Hospital of Leuven, Belgium; ²³Department of Hematology, Academische Ziekenhuis, Maastricht, the Netherlands; ²⁴Department of Hematology, Hopital Saint Louis, Paris, France; ²⁵Department of Medicine, University of Calgary, AB, Canada; ²⁶Isala Clinics Zwolle, the Netherlands; ²⁷Division of Hematology and Oncology, Washington University School of Medicine, St. Louis, MO, USA; ²⁸Division of Hematology/Oncology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA; ²⁹Division of Hematology/Oncology & HSCT, The Center for Cancer and Blood Disorders, Children's Hospital/Louisiana State University Medical Center, New Orleans, LA, USA; ³⁰Division of Clinical Hematology, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; ³¹Thomas Jefferson University Hospital, Philadelphia, PA, USA; ³²Cincinnati Children's Hospital Medical Center, OH, USA; ³³Hematologic Malignancies & Bone Marrow Transplant, Department of Medical Oncology, New York Presbyterian Hospital/Weill Cornell Medical Center, NY, USA; ³⁴The Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, GA, USA; ³⁵Dana Farber Cancer Institute/ Boston Children's Hospital, MA, USA; ³⁶Department of Pediatric Hematology, Oncology and Bone Marrow Transplant, British Columbia's Children's Hospital, The University of British Columbia, Vancouver, BC, Canada; ³⁷Division of Bone Marrow Transplant, Seattle Cancer Care Alliance, WA, USA; ³⁸CIBMTR (Center for International Blood and Marrow Transplant Research), National Marrow Donor Program/Be the Match, Minneapolis, MN, USA and ³⁹Division of Hematology, Oncology, and Transplantation, Department of Medicine, University of Minnesota Medical Center, Minneapolis, MN, USA

©2017 Ferrata Storti Foundation. This is an open-access paper. doi:10.3324/haematol.2016.156356

Received: September 16, 2016.

Accepted: March 7, 2017.

Pre-published: March 16, 2017.

Correspondence: joseph.pidala@moffitt.org

Supplementary table 1: Characteristics of aGVHD-related variables for patients who developed aGVHD Grade II receiving cyclosporine-based GVHD prophylaxis

Variable	1999-2001	2002-2005	2006-2012
Number of CsA patients*	163	260	136
aGVHD organ involvement			
Skin + Liver + UGI + LGI	1 (<1)	1 (<1)	1 (<1)
Skin + Liver + UGI	2 (1)	10 (4)	1 (<1)
Skin + Liver + LGI	14 (9)	6 (2)	2 (1)
Skin + UGI + LGI	1 (<1)	6 (2)	15 (11)
Skin + UGI	7 (4)	44 (17)	21 (15)
Skin + LGI	43 (26)	36 (14)	20 (15)
Skin + Liver	18 (11)	15 (6)	9 (7)
Liver + UGI + LGI	0	1 (<1)	0
Liver + UGI	1 (<1)	3 (1)	0
Liver + LGI	3 (2)	1 (<1)	0
UGI + LGI	1 (<1)	1 (<1)	10 (7)
Skin	47 (29)	88 (34)	32 (24)
UGI	11 (7)	32 (12)	14 (10)
LGI	13 (8)	13 (5)	8 (6)
Liver	1 (<1)	3 (1)	3 (2)
aGVHD treatment (summary categories)			
Steroids + ATG +- others	2 (1)	8 (3)	0
Steroids + MAB +- others	6 (4)	15 (6)	8 (6)
Steroids +- others	147 (90)	221 (85)	117 (86)
Missing	8 (5)	16 (6)	11 (8)
aGVHD treatment (detail)			
Steroids + ATG +- others	2 (1)	8 (3)	0
Steroids + MAB +- others	6 (4)	15 (6)	8 (6)
Steroids only	19 (12)	14 (5)	20 (15)
Steroids + CsA only	87 (53)	137 (53)	38 (28)
Steroids + CsA + MMF +- others	8 (5)	25 (10)	24 (18)
Steroids + CsA + MTX +- others	5 (3)	4 (2)	3 (2)
Steroids + CsA + others	19 (12)	26 (10)	16 (12)
Steroids + Tac only	3 (2)	9 (3)	0
Steroids + Tac + MMF +- others	0	3 (1)	5 (4)
Steroids + Tac + others	0	0	1 (<1)
Steroids + others	6 (4)	3 (1)	10 (7)
Missing	8 (5)	16 (6)	11 (8)

Variable	1999-2001	2002-2005	2006-2012
Cause of death			
Number of deaths	104	153	86
Primary disease	46 (44)	70 (46)	44 (51)
New malignancy	4 (4)	2 (1)	0
GVHD	7 (7)	20 (13)	9 (10)
IPN	8 (8)	10 (7)	2 (2)
Infection	14 (13)	23 (15)	11 (13)
Organ failure	14 (13)	13 (8)	14 (16)
Other cause	10 (10)	10 (7)	6 (7)
Missing	1 (<1)	5 (3)	0

*: Includes n=46 patients who received CsA & Tac as a part of GVHD prophylaxis.

Supplementary table 2: Characteristics of aGVHD-related variables for patients who developed aGVHD Grade II receiving tacrolimus-based GVHD prophylaxis

Variable	1999-2001	2002-2005	2006-2012
Number of Tac patients	54	238	741
aGVHD organ involvement			
Skin + Liver + UGI + LGI	0	2 (<1)	8 (1)
Skin + Liver + UGI	0	1 (<1)	4 (<1)
Skin + Liver + LGI	0	3 (1)	4 (<1)
Skin + UGI + LGI	1 (2)	4 (2)	93 (13)
Skin + UGI	4 (7)	38 (16)	119 (16)
Skin + LGI	11 (20)	35 (15)	105 (14)
Skin + Liver	3 (6)	6 (3)	11 (1)
Liver + UGI + LGI	0	0	4 (<1)
Liver + UGI	0	0	2 (<1)
Liver + LGI	0	1 (<1)	2 (<1)
UGI + LGI	1 (2)	4 (2)	86 (12)
Skin	29 (54)	90 (38)	144 (19)
UGI	0	36 (15)	99 (13)
LGI	5 (9)	18 (8)	52 (7)
Liver	0	0	8 (1)
aGVHD treatment (summary categories)			
Steroids + ATG +- others	3 (6)	7 (3)	9 (1)
Steroids + MAB +- others	5 (9)	22 (9)	52 (7)
Steroids +- others	45 (83)	202 (85)	645 (87)
Missing	1 (2)	7 (3)	35 (5)
aGVHD treatment (detail)			
Steroids + ATG +- others	3 (6)	7 (3)	9 (1)
Steroids + MAB +- others	5 (9)	22 (9)	52 (7)
Steroids only	4 (7)	20 (8)	87 (12)
Steroids + CsA	0	1 (<1)	3 (<1)
Steroids + CsA + MMF +- others	0	2 (<1)	6 (<1)
Steroids + CsA + others	1 (2)	2 (<1)	4 (<1)
Steroids + Tac	21 (39)	99 (42)	207 (28)
Steroids + Tac + MMF +- others	6 (11)	48 (20)	124 (17)
Steroids + Tac + MTX +- others	1 (2)	3 (1)	15 (2)
Steroids + Tac + others	6 (11)	19 (8)	147 (20)
Steroids + others	6 (11)	8 (3)	52 (7)
Missing	1 (2)	7 (3)	35 (5)

Cause of death

Number evaluable	39	156	373
Primary disease	17 (44)	73 (47)	193 (52)
New malignancy	0	4 (3)	5 (1)
GVHD	1 (3)	18 (12)	52 (14)
IPN	4 (10)	11 (7)	11 (3)
Infection	7 (18)	15 (10)	41 (11)
Organ failure	8 (21)	14 (9)	38 (10)
Other cause	2 (5)	17 (11)	18 (5)
Missing	0	4 (3)	15 (4)

Supplemental table 3: Characterization of included acute GVHD cases for both cyclosporine and tacrolimus groups according to refined Minnesota risk classification

Variable	Cyclosporine			Tacrolimus		
	1999-2001	2002-2005	2006-2012	1999-2001	2002-2005	2006-2012
Number of overall patients	359	473	245	132	472	1163
aGVHD grade						
II	163 (45)	260 (55)	136 (56)	54 (41)	238 (50)	741 (64)
III	140 (39)	151 (32)	72 (29)	46 (35)	152 (32)	286 (25)
IV	56 (16)	62 (13)	37 (15)	32 (24)	82 (17)	136 (12)
Standard/High Risk aGVHD						
Standard Risk	198 (55)	287 (61)	151 (62)	73 (55)	290 (61)	741 (64)
High Risk	161 (45)	186 (39)	94 (38)	59 (45)	182 (39)	422 (36)
Number of grade II patients	163	260	136	54	238	741
Standard/High Risk aGVHD						
Standard Risk	140 (86)	231 (89)	123 (90)	53 (98)	229 (96)	635 (86)
High Risk	23 (14)	29 (11)	13 (10)	1 (2)	9 (4)	106 (14)
Number of grade III-IV patients	196	213	109	78	234	422
aGVHD grade						
III	140 (71)	151 (71)	72 (66)	46 (59)	152 (65)	286 (68)
IV	56 (29)	62 (29)	37 (34)	32 (41)	82 (35)	136 (32)
Standard/High Risk aGVHD						
Standard Risk	58 (30)	56 (26)	28 (26)	20 (26)	61 (26)	106 (25)
High Risk	138 (70)	157 (74)	81 (74)	58 (74)	173 (74)	316 (75)