

TITLE

Possible role of highly activated mucosal NK cells against viral respiratory infections in children undergoing haematopoietic stem cell transplantation

AUTHORS

Maria Vela^{*1}, Teresa del Rosal^{*2}, Antonio Pérez-Martínez^{#3}, Jaime Valentín⁴, Inmaculada Casas⁵, Francisco Pozo⁶, Francisco Reinoso-Barbero⁷, David Bueno⁸, Dolores Corral⁹, Ana Méndez-Echevarría¹⁰, Yasmina Mozo¹¹, Cristina Calvo¹².

1. Maria Vela^{*} PhD; Translational Research in Paediatric Oncology, Hematopoietic Transplantation & Cell Therapy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain. maria.vela@idipaz.es
2. Teresa del Rosal^{*} MD, PhD; Paediatric Infectious Diseases Department, La Paz University Hospital, Madrid, Spain; Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain. teredelrosal@yahoo.es
3. Antonio Pérez-Martínez[#] MD, PhD; Paediatric Hemato-Oncology Department, La Paz University Hospital, Madrid, Spain; Translational Research in Paediatric Oncology, Hematopoietic Transplantation & Cell Therapy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain. aperezmartinez@salud.madrid.org
4. Jaime Valentín MSc; Translational Research in Paediatric Oncology, Hematopoietic Transplantation & Cell Therapy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain. jaimevquirola@hotmail.com
5. Inmaculada Casas PhD. Respiratory Virus and Influenza Unit, National Microbiology Center (ISCIII), Madrid, Spain. icasas@isciii.es
6. Francisco Pozo PhD. Respiratory Virus and Influenza Unit, National Microbiology Center (ISCIII), Madrid, Spain. pacopozo@isciii.es

7. Francisco Reinoso-Barbero MD, PhD; Pediatric Anesthesiology Department, La Paz University Hospital, Madrid, Spain. francisco.reinoso@salud.madrid.org
8. David Bueno MD; Paediatric Hemato-Oncology Department, La Paz University Hospital, Madrid, Spain. david.bueno@salud.madrid.org
9. Dolores Corral MD, PhD; Paediatric Hemato-Oncology Department, La Paz University Hospital, Madrid, Spain. mariadolores.corral@salud.madrid.org
10. Ana Méndez-Echevarría MD, PhD; Paediatric Infectious Diseases Department, La Paz University Hospital, Madrid, Spain; Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain. amendezes@yahoo.es
11. Yasmina Mozo MD; Paediatric Hemato-Oncology Department, La Paz University Hospital, Madrid, Spain. yasmina.mozo@salud.madrid.org
12. Cristina Calvo MD, PhD; Paediatric Infectious Diseases Department, La Paz University Hospital, Madrid, Spain; Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain. Translational Research Network in Pediatric Infectious Diseases (RITIP), Madrid, Spain. TEDDY Network (European Network of Excellence for Paediatric Clinical Research), Italy. ccalvorey@gmail.com

* These authors contributed equally to this work.

Corresponding Author Address:

Antonio Pérez-Martínez MD, PhD. Paediatric Hemato-Oncology Department. La Paz University Hospital. Paseo de la Castellana, 261, Madrid, 28046, Spain. Phone: +34917277223; fax: +34917277042. Email: aperezmartinez@salud.madrid.org

Supplementary Table 1. T cell and NK cell counts in patients' NPAs.

	pre-HSCT (total cell counts)	Day 0 (total cell counts)	Day 10 (total cell counts)	Day 20 (total cell counts)	Day 30 (total cell counts)
T	294, 614-45	361, 1827-6	56, 296-25	56, 366-35	65, 242-32
NK	26, 60-9	38, 56-20	46, 69-20	26, 51-16	13, 84-11

	pre-HSCT (total cell counts)	Day 0 (total cell counts)	Day 10 (total cell counts)	Day 20 (total cell counts)	Day 30 (total cell counts)
T_PCR-	294, 610-82	532, 1827-338	116, 362-49	366, 423-309	59, 279-5
T_PCR+	294, 626-32	7, 2103-4	25, 52-17	38, 52-22	135, 206-65
p value	0.624	0.343	0.133	0.057	0.800

	pre-HSCT (total cell counts)	Day 0 (total cell counts)	Day 10 (total cell counts)	Day 20 (total cell counts)	Day 30 (total cell counts)
NK_PCR-	18, 27-6	44, 56-11	40, 58-15	21, 44-14	13, 79-10
NK_PCR+	80, 143-50	34, 60-22	69, 69-47	51, 51-26	51, 90-12
p value	0.005	0.960	0.164	0.143	0.800

Data are median, IQR.

Abbreviations: NK_PCR-, NK cell count in HSCT recipients without viral respiratory infection; NK_PCR+, NK cell count in HSCT recipients with viral respiratory infection; T_PCR-, T cell count in HSCT recipients without viral respiratory infection; T_PCR+, T cell count in HSCT recipients with viral respiratory infection.

Supplementary Table 2. T cell and NK cell counts in patients' PB.

	pre-HSCT (cells/ μ l)	Day 15 (cells/ μ l)	Day 30 (cells/ μ l)
T	1127, 2263-591	113, 415-6	306, 538-143
NK	128, 192-68	66, 194-23	122, 325-65

	pre-HSCT (cells/ μ l)	Day 15 (cells/ μ l)	Day 30 (cells/ μ l)
T_PCR-	954, 1751-249	129, 391-7	238, 408-93
T_PCR+	2014, 3677-1090	63, 846-3	448, 596-314
p value	0.071	0.929	0.210

	pre-HSCT (cells/ μ l)	Day 15 (cells/ μ l)	Day 30 (cells/ μ l)
NK_PCR-	111, 185-62	63, 140-17	168, 348-99
NK_PCR+	154, 225-61	78, 272-25	82, 111-56
p value	0.616	0.374	0.085

Data are median, IQR.

Abbreviations: NK_PCR-, NK cell count in HSCT recipients without viral respiratory infection; NK_PCR+, NK cell count in HSCT recipients with viral respiratory infection; T_PCR-, T cell count in HSCT recipients without viral respiratory infection; T_PCR+, T cell count in HSCT recipients with viral respiratory infection.

Supplementary Table 3. NPA T cell reconstitution versus outcome.

	pre-HSCT (total cell counts)	Day 0 (total cell counts)	Day 10 (total cell counts)	Day 20 (total cell counts)	Day 30 (total cell counts)
No acute GVHD	86, 580-7 (12)	11, 1046-4 (8)	36, 53-15 (8)	211, 534-50 (4)	65 (1)
Acute GVHD	294, 309-110 (7)	384, 396-349 (3)	80, 116-52 (3)	18, 30-9 (3)	5 (1)
p value	0.605	0.630	0.303	0.114	-
<hr/>					
No Chronic GVHD	141, 547-41 (17)	164, 402-6 (10)	36, 73-19 (10)	38, 52-22 (6)	35, 50-20 (2)
Chronic GVHD	348, 293-238 (2)	2800.0 (1)	56.0 (1)	1038.0 (1)	-
p value	0.632	-	-	-	-
<hr/>					
No graft failure	134, 489-41 (18)	13, 384-5 (9)	36, 55-19 (10)	38, 285-22 (6)	35, 50-20 (2)
Graft failure	690 (1)	1436, 1826-1046 (2)	296 (1)	56 (1)	-
p value	-	0.146	-	-	-
<hr/>					
No ICU admission	80, 431-24 (15)	10, 164-4 (7)	47, 56-17 (9)	42, 366-35 (5)	35, 50-20 (2)
ICU admission	492, 698-255 (4)	532, 1046-402 (4)	160, 228-92 (2)	28, 42-14 (2)	-
p value	0.077	0.073	0.455	0.571	-
<hr/>					
Alive	62, 489-15 (14)	10, 164-4 (7)	36, 53-16 (8)	42, 366-35 (5)	35, 50-20 (2)
Dead	303, 690-294 (5)	532, 1046-402 (4)	80, 188-52 (3)	28, 42-14 (2)	-
p value	0.066	0.073	0.206	0.571	-

Data are summarized as median, IQR (n).

Abbreviations: HSCT: haematopoietic stem cell transplantation; GVHD, graft versus host disease; ICU, intensive care unit.

Supplementary Table 4. NPA NK cell reconstitution versus outcome.

	pre-HCT (total cell counts)	Day 0 (total cell counts)	Day 10 (total cell counts)	Day 20 (total cell counts)	Day 30 (total cell counts)
No acute GVHD	44, 81-14 (12)	30, 44-20 (6)	43, 52-16 (8)	25, 32-25 (4)	12.0 (1)
Acute GVHD	20, 38-8 (7)	44, 53-37 (3)	57, 63-51 (3)	16, 33-12 (3)	79.0 (1)
p value	0.253	0.417	0.511	0.714	-
<hr/>					
No Chronic GVHD	28, 60-11 (17)	38, 30-30 (10)	47, 69-40 (10)	25, 44-18 (6)	45, 62-28 (2)
Chronic GVHD	78, 115-41 (2)	20.0 (1)	13.0 (1)	14.0 (1)	-
p value	0.983	-	-	-	-
<hr/>					
No graft failure	32, 75-9 (18)	41, 53-30 (10)	47, 69-40 (9)	20, 25-14 (6)	45, 62-28 (2)
Graft failure	28 (1)	11, 15-6 (2)	10 (1)	51 (1)	-
p value	-	0.067	-	-	-
<hr/>					
No ICU admission	39, 83-9 (15)	44, 59-32 (7)	47, 69-40 (9)	25, 26-14 (5)	45, 62-28 (2)
ICU admission	24, 36-17 (4)	25, 33-15 (4)	10.0 (1)	33, 42-24 (2)	-
p value	0.866	0.152	-	0.619	-
<hr/>					
Alive	44, 85-10 (14)	44, 59-32 (7)	47, 69-34 (8)	25, 26-14 (5)	45, 62-28 (2)
Dead	20, 28-11 (5)	25, 33-15 (4)	28, 37-19 (3)	33, 42-24 (2)	-
p value	0.331	0.152	0.200	0.619	-

Data are summarized as median, IQR (n).

Abbreviations: HSCT: haematopoietic stem cell transplantation; GVHD, graft versus host disease; ICU, intensive care unit.