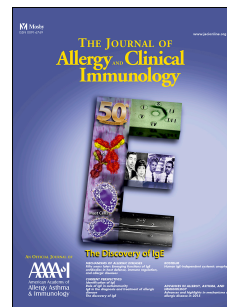


# Accepted Manuscript

Non-PTLD Malignancy post HSCT in patients with Primary Immunodeficiency: UK experience

Mohamed Najib Mohamed Unni, M.MED, Reem Elfeky, MD, Kanchan Rao, MD, Zohreh Nademi, PhD, Robert Chiesa, MD, Persis Amrolia, PhD, Roderick Skinner, PhD, Olga Slater, PhD, Austen Worth, PhD, Terence Flood, MD, Mario Abinun, MD, Sophie Hambleton, DPhil, Waseem Qasim, PhD, Hubert B. Gaspar, PhD, Andrew J. Cant, MD, Andrew R. Gennery, MD, Paul Veys, MD, Mary A. Slatter, MD



PII: S0091-6749(18)30391-9

DOI: [10.1016/j.jaci.2018.02.038](https://doi.org/10.1016/j.jaci.2018.02.038)

Reference: YMAI 13354

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 14 November 2017

Revised Date: 14 February 2018

Accepted Date: 16 February 2018

Please cite this article as: Unni MNM, Elfeky R, Rao K, Nademi Z, Chiesa R, Amrolia P, Skinner R, Slater O, Worth A, Flood T, Abinun M, Hambleton S, Qasim W, Gaspar HB, Cant AJ, Gennery AR, Veys P, Slatter MA, Non-PTLD Malignancy post HSCT in patients with Primary Immunodeficiency: UK experience, *Journal of Allergy and Clinical Immunology* (2018), doi: 10.1016/j.jaci.2018.02.038.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1 **Non-PTLD Malignancy post HSCT in patients with Primary**

2 **Immunodeficiency: UK experience**

3

4 **Authors**

5 Mohamed Najib Mohamed Unni M.MED<sup>1</sup>, Reem Elfeky MD<sup>2</sup>, Kanchan Rao MD<sup>2</sup>,  
6 Zohreh Nademi PhD<sup>1</sup>, Robert Chiesa MD<sup>2</sup>, Persis Amrolia PhD<sup>2</sup>, Roderick Skinner  
7 PhD<sup>1</sup>, Olga Slater PhD<sup>2</sup>, Austen Worth PhD<sup>2</sup>, Terence Flood MD<sup>1</sup>, Mario Abinun  
8 MD<sup>1</sup>, Sophie Hambleton DPhil<sup>1,3</sup>, Waseem Qasim PhD<sup>2</sup>, Hubert B.Gaspar PhD<sup>2</sup>,  
9 Andrew J. Cant MD<sup>1</sup>, Andrew R. Gennery MD<sup>1,3</sup>, Paul Veys MD<sup>2</sup>, Mary A. Slatter  
10 MD<sup>1,3</sup>

11

12 **Institutions**

- 13 1. Children's Haemopoietic Stem Cell Transplant Unit, Great North Children's  
14 Hospital, Newcastle upon Tyne Hospital NHS Foundation Trust, UK  
15 2.Great Ormond Street Hospital NHS Trust, London, UK  
16 3. Institute of Cellular Medicine, Newcastle University, UK

17

18 **Corresponding author**

19 Dr M.A. Slatter,  
20 Paediatric Immunology, Infectious Diseases & Allergy Department  
21 Clinical Resource Building, Block 2, Level 4  
22 Royal Victoria Infirmary, Queen Victoria Road  
23 Newcastle upon Tyne, NE1 4LP, UK  
24 e-mail: [mary.slatter@nuth.nhs.uk](mailto:mary.slatter@nuth.nhs.uk)  
25 Phone: 0191 2823767 Fax: 0191 2820497

26 There was no specific funding for this study.

27 Conflict-of-interest disclosure: The authors declare no competing financial

28 interests.

29

30 **Short summary**

31 Secondary malignancy post haematopoietic stem cell transplantation (HSCT) for

32 malignant disorders is well recognized. There are very few published reports on

33 malignancy post HSCT for Primary Immunodeficiency (PID). We report 12 cases

34 of 944 patients, who developed non-PTLD malignancy post-HSCT for PID.

35

36 **Key words**

37 Primary Immunodeficiency; HSCT; non-PTLD malignancy

38 **To the Editor**

39

40 Secondary malignancy post-haematopoietic stem cell transplantation  
41 (HSCT) for malignant disorders related to cytotoxic treatment, radiotherapy and  
42 pre-existing genetic pre-disposition, is well recognized. Data regarding the  
43 incidence of malignancy in normal children and in those post-HSCT for  
44 haematological disorders can be found in the online repository.

45 Some non-malignant disorders may predispose to malignancy as seen in  
46 cases with Fanconi anaemia developing squamous cell carcinoma of head, neck  
47 and anogenital mucosal surfaces particularly if graft-versus-host disease (GVHD)  
48 occurs. Post transplant lymphoproliferative disorders (PTLDs) usually in  
49 association with Epstein Barr virus (EBV), may occur after HSCT for any  
50 underlying diagnosis, usually within 2 years post-transplant, most often  
51 associated with T-lymphocyte depletion (TCD) and intense immunosuppression,  
52 for example in the context of GVHD<sup>1</sup>. Data are sparse on occurrence of non-PTLD  
53 malignancy post-HSCT in patients with primary immunodeficiencies (PID). PID  
54 are an heterogenous group of disorders affecting the regulation and function of  
55 the immune system. To date, more than 300 genetic defects cause different  
56 disease phenotypes. It is estimated that the risk of malignancy in children with  
57 PID is about 4%, 10 000 times greater than in age-matched controls<sup>2</sup>. HSCT can  
58 cure PID, and reduce the risk of malignancy, but it is unknown whether HSCT  
59 itself might increase the incidence of malignancy compared to the normal  
60 population. Fifty-two post HSCT malignancies were confirmed in a large study of  
61 2266 patients with PID including 45 PTLDs. Three patients developed  
62 myelodysplastic syndrome (MDS) all of whom had received TBI and TCD grafts, 1

63 patient developed acute myeloid leukaemia (AML) and 3 developed solid  
64 tumours giving an incidence of 0.3% of non-PTLD malignancy<sup>3</sup>. Six malignancies  
65 were reported from 318 patients who underwent allogeneic HSCT for non-  
66 malignant disorders, including 2 solid tumours in 130 patients with PID (1 with  
67 Severe combined immunodeficiency (SCID) and 1 with Chronic granulomatous  
68 disease)<sup>4</sup>.

69 We report a retrospective analysis of 944 children who underwent HSCT  
70 for PID at two UK centers. Diagnosis, timing and type of transplant, conditioning  
71 regimen, GVHD, viral reactivation, type of malignancy and outcome were  
72 recorded.

73 Twelve patients (1.27%) developed non-PTLD malignancy (Table 1).  
74 Median interval from HSCT to malignancy diagnosis was 3.75 years (3 months –  
75 11.2 years). Mean age at transplant in those who developed malignancy was 85  
76 months (4 months – 204 months). Four received an HLA matched sibling donor  
77 (MSD) bone marrow (BM) transplant, 4 had matched and 1 mismatched  
78 unrelated donor BM, 2 matched unrelated donor PBSC and 1 matched cord blood  
79 transplant.

80 None of the patients received radiotherapy. Seven had reduced intensity  
81 conditioning (RIC) with fludarabine and melphalan, 3 had reduced toxicity  
82 myeloablative conditioning with treosulfan and fludarabine, 2 had myeloablative  
83 doses of busulfan, 1 with cyclophosphamide(n=1), the other with fludarabine  
84 (n=1). Ten received serotherapy with Alemtuzumab and 2 MSD recipients had no  
85 serotherapy. All patients received cyclosporine based GVHD prophylaxis either  
86 alone (n=2) or with mycophenolate mofetil ( P1-5,7,8 and 11) or methotrexate

87 (P9,P12).

88 Two patients died from malignancy. The rest were successfully treated  
89 and are alive with a median follow up of 13.2 years ( 2 years 1 mth – 18 years).

90 Both P1 and P12 had lost donor engraftment in whole blood or B  
91 cell/myeloid subsets before the onset of Philadelphia positive acute  
92 lymphoblastic leukemia (P1) and Juvenile Myelomonocytic Leukemia (P12)  
93 respectively. Both malignancies were confirmed to be recipient in origin. Both  
94 had an underlying immune defect that predisposes to malignancy (RAG 2 in P1,  
95 Griscelli syndrome in P12). This poses the question as to whether full donor  
96 chimerism might have abolished this risk. Alternatively recipient stem cells  
97 surviving chemotherapy may have acquired genotoxic insults.

98 P9 developed Acute Myeloid Leukemia (AML M4) 11 years post-HSCT  
99 which is uncommon. Unfortunately, it was undetermined whether leukemic cells were  
100 donor or recipient origin. A European Bone Marrow Transplantation group survey  
101 estimated incidence of MDS/AML to be 1.2:1000 transplants, mostly occurring  
102 within 4 years of HSCT (See OR)<sup>E6</sup>. Multiple hit theory postulates that donor cells  
103 already acquired a first hit in the donor and additional hits are acquired in the host  
104 marrow microenvironment. Viral persistence, disturbed immunosurveillance and  
105 accelerated telomere shortening may also be contributory<sup>6,7</sup>.

106 P2 and P5 developed parotid muco-epidermoid carcinoma (MEC) at 6 and  
107 3 years post-HSCT. Interestingly both experienced oral cGVHD and had  
108 prolonged HHV6 viraemia post-HSCT. Data link parotid MEC to prolonged CMV  
109 infection, which remains dormant in the salivary glands<sup>8</sup>. Presence of HHV6 in an

110 immunocompromised host might have played a role in the development of this  
111 rare tumour.

112 P7 had fungal granuloma pre-transplant, received voriconazole  
113 throughout transplant and developed actinic keratosis, a pre-malignant  
114 condition and later squamous cell carcinoma of the lower leg and auricular basal  
115 cell carcinoma. A retrospective study confirmed the association between  
116 voriconazole and the development of squamous cell carcinoma post-allogenic  
117 HSCT<sup>9</sup>.

118 P8 and P11 had a family history of solid tumor suggesting possible genetic  
119 factors. P2,5,7 and 11 experienced acute GVHD and P11 additionally  
120 experienced chronic GVHD. Immune dysregulation post-HSCT might have played  
121 a role in the failure of T-lymphocyte checkpoint for tumors.

122 Whilst early haematological malignancies likely relate to the pre-existing  
123 genotype in remaining recipient cells, most of our patients developed late rare  
124 solid tumors. Understanding the pathogenesis of solid tumors after HSCT is  
125 limited, but intensive cytotoxic conditioning with defective DNA repair of  
126 persisting stem cells/stromal cells, viral infection and immunosuppression may  
127 be implicated. All patients in this cohort received alkylating agents during  
128 conditioning. These agents induce chromosomal breakage and possible  
129 malignant transformation. Over the last 15 years the use of RIC and reduced  
130 toxicity conditioning has increased but it is unknown whether this will reduce  
131 the risk of malignancy post-HSCT. Fludarabine-based conditioning, moderate-  
132 severe chronic GVHD and chronic myeloproliferative or non-malignant disease  
133 are risk factors for second malignancy in adult patients<sup>5,6</sup>. Shimoni et al found no  
134 significant difference in the incidence of secondary malignancies in 931 adults

135 receiving myeloablative, reduced intensity or reduced toxicity conditioning and  
136 postulated that there may be synergistic effects of DNA damage from an  
137 alkylator added to fludarabine related inhibition of DNA repair used in reduced  
138 intensity or toxicity regimens<sup>6</sup>.

139 In conclusion we report an incidence of 1.27% non-PTLD malignancy  
140 occurring in a large cohort of PID patients who received cytotoxic chemotherapy  
141 without radiotherapy for HSCT. This incidence is higher than that reported by  
142 Kamani et al. which may be due to the smaller number of patients. Underlying  
143 genetic disease, tissue distribution of genetic defect, GvHD, viral infections and  
144 extent of donor chimerism may be important factors that play a role in primary  
145 immunodeficiency patients developing secondary malignancies post-HSCT.  
146 Further studies are needed to evaluate risks but we support recommendations  
147 for life-long follow up for this population.

148

#### 149 **Authors**

150

151 Mohamed Najib Mohamed Unni M.MED<sup>1</sup>,

152 Reem Elfeky MD<sup>2</sup>,

153 Kanchan Rao MD<sup>2</sup>,

154 Zohreh Nademi PhD<sup>1</sup>,

155 Robert Chiesa MD<sup>2</sup>,

156 Persis Amrolia PhD<sup>2</sup>,

157 Roderick Skinner PhD<sup>1</sup>,

158 Olga Slater, PhD<sup>2</sup>

159 Austen Worth PhD<sup>2</sup>,

160 Terence Flood MD<sup>1</sup>,



161 Mario Abinun MD<sup>1</sup>,  
162 Sophie Hambleton DPhil<sup>1,3</sup>,  
163 Waseem Qasim PhD<sup>2</sup>,  
164 Hubert B.Gaspar PhD<sup>2</sup>,  
165 Andrew J. Cant MD<sup>1</sup>,  
166 Andrew R. Gennery MD<sup>1,3</sup>,  
167 Paul Veys MD<sup>2</sup>,  
168 Mary A. Slatter MD<sup>1,3</sup>

169 **Institutions**

- 170 1. Children's Haemopoietic Stem Cell Transplant Unit, Great North Children's  
171 Hospital, Newcastle upon Tyne Hospital NHS Foundation Trust, UK  
172 2.Great Ormond Street Hospital NHS Trust, London, UK  
173 3. Institute of Cellular Medicine, Newcastle University, UK

174

175 **References :**

176  
177  
178

- 179 1. Bomken S, Skinner R. Secondary Malignant Neoplasms Following  
180 Haematopoietic Stem Cell Transplantation in Childhood. Children. 2015;2:  
181 146-173  
182  
183 2. McClain KL. Immunodeficiency states and related malignancies. Cancer  
184 Treat Res. 1997;92:39-61.  
185  
186 3. Kamani NR, Kumar S, Hassebroek A, Eapen M, LeRademacher J, Casper J et  
187 al. Malignancies after hematopoietic cell transplantation for primary  
188 immune deficiencies: a report from the Center for International Blood and

- 189 Marrow transplant Research. Biol Blood Marrow Transplant 2011;  
190 17(12):1783-1789  
191
- 192 4. Nelson AS, Vadjic CM, Ashton LJ , Marsney REL , Smith IN, Wilcox L et al.  
193 Incident cancers and late mortality in Australian children treated by  
194 allogeneic stem cell transplantation for non-malignant diseases. Pediatr  
195 Blood Cancer 2017; 64:197-202
- 196 5. Eapen M, Woo Ahn K, Orchard PJ, Cowan MJ, Davies SM , Fasth A et al.  
197 Long-term survival and late deaths after hematopoietic cell  
198 transplantation for primary immunodeficiency diseases and inborn  
199 errors of metabolism. BBMT 2012; 18:1438-1445
- 200 6. Shimoni A, Shem-Tov N, Chetrit A , Volchek Y, Tallis E, Avigdor A et al.  
201 Secondary malignancies after allogeneic stem-cell transplantation in the  
202 era of reduced-intensity conditioning; the incidence is not reduced.  
203 Leukemia 2013, 27, 829–835
- 204 7. Wiseman DH, Donor cell leukemia : a review. Biol Blood Marrow  
205 Transplant 2011:17:771-789
- 206 8. Melnick M, Sedghizadeh PP, Allen CM, Jaskoll T. Human cytomegalovirus  
207 and mucoepidermoid carcinoma of salivary glands:Cell-specific  
208 localization of active viral and oncogenic signaling proteins is  
209 confirmatory of a causal relationship. Experimental and Molecular  
210 Pathology 2012;92(1):118-125
- 211 9. Wojenski DJ, Bartoo GT, Merten JA, Dierkhising RA, Barajas MR,El-Azhary

212 RA et al. Voriconazole exposure and the risk of cutaneous squamous cell  
 213 carcinoma in allogenic hematopoietic stem cell transplant patients.

214 Transplant Infectious Disease 2015 April : 17(2) : 250-258

215

216

217

218

219

220 **Table I. Patient characteristics**

Diagnosis Lineage specificity of gene defect	Age at HSCT (years)	Conditioning Regimen	Source of stem cells	Chimerism T/B/Myeloid (%)	Malignancy	Interval post HSCT (years)	Acute/ Chronic GVHD	Auto- immunity	Viral react- ivation	Status
1.RAG 2 SCID lymphocyte- specific	0.3	T 36g/m <sup>2</sup> F 150mg/m <sup>2</sup>	MSD BM	100/0/0	Ph+ Pre B ALL	2.5	No	No	No	Died
2.MHC 1 systemic	13.6	F150mg/m <sup>2</sup> Mel140mg/m <sup>2</sup> AI 1mg/kg	MUD BM	100/100/100	Parotid MEC	6	Acute Skin & oral GVHD	No	HHV6	Alive
3.GATA 2 systemic	15.9	F150mg/m <sup>2</sup> Mel140g/m <sup>2</sup> AI 1 mg/kg	MMUD BM	94/100/100	Toe Melanoma	6.9	No	No	No	Alive
4.JAK 3 SCID lymphocyte- specific	0.1	T36g/m <sup>2</sup> F150mg/m <sup>2</sup> AI 0.3mg/kg	Matched UCB	100/97/93	Right Occipital Ewing Sarcoma	3.58	No	No	No	Alive
5.NFKB2 systemic	14	F150mg/m <sup>2</sup> Mel140mg/m <sup>2</sup> AI 1mg/kg	MSD BM	100/100/100	Parotid MEC	3	Acute Skin Grade II and Liver Grade I GVHD + Oral GVHD	No	HHV6	Alive
6.WAS hematopoietic	17	F150mg/m <sup>2</sup> Mel140mg/m <sup>2</sup> AI 1mg/kg	MUD BM	100/100/100	Squamous cell ca (gastrostomy site)	0.25	No	No	EBV	Alive
7.X linked-CGD myeloid specific	15	F160mg/m <sup>2</sup> Bu12.8mg/kg AI 1mg/kg	MUD PBSC	100/100/100	Basal cell ca (ear) and left lower leg squamous cell carcinoma in situ	4	Acute Skin Grade I	No	No	Alive
8.CD40 ligand T-lymphocyte- specific	1.8	F150mg/m <sup>2</sup> Mel140mg/m <sup>2</sup> AI 1mg/kg	MUD PBSC	34/0/9	Renal cell ca	4.8	No	Auto- immune neutron- penia	Adeno	Alive

9.T+B+NK low SCID unknown	1.0	Bu 12.8mg/kg Cy 200mg/kg AI 1mg/kg	MUD BM	96 Whole blood	AML	11	No	No	No	Alive
10.LAD1 systemic	1.4	F150mg/m <sup>2</sup> Mel140mg/m <sup>2</sup> AI 1mg/kg	MUD BM	100/100/100	Renal Cell Ca	11.2	No	Immune thrombocytopenia	No	Alive
11.T-B+NK+ SCID unknown	4.4	F 150mg/m <sup>2</sup> Mel 140mg/m <sup>2</sup> AI 0.6mg/kg	MSD BM	100/100/100	Embryonal RMS of right cheek	0.45	Acute GVHD- Skin Grade 3, Liver Grade 2, Gut Grade 2 - II Chronic GVHD - gut	No	Adeno Varicella	Alive
12.GrisCELLI/HLH systemic	0.7	T 42g/m <sup>2</sup> F 150mg/m <sup>2</sup>	MSD BM	0 whole blood	JMML	0.78	No	No	Adeno	Died

221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232

T = Treosulfan, F= Fludarabine, AI =Alemtuzumab, Mel = Melphalan, Bu = Busulfan, Cy =Cyclophosphamide, MSD = matched sibling donor, UCB = Unrelated Cord Blood, MUD = Matched Unrelated Donor, BM = bone marrow, MMUD = mismatched unrelated donor, PBSC = Peripheral Blood Stem Cells, ALL = acute lymphocytic leukaemia, JMML = Juvenile Myelomonocytic Leukemia, AML = Acute Myeloid Leukemia, RMS= Rhabdomyosarcoma, Ca = Carcinoma, MEC = Mucoepidermoid Carcinoma, T=T Lymphocyte, B=B Lymphocyte, NK= Natural Killer, SCID =Severe Combined Immunodeficiency, MHC I =Major Histocompatibility Complex I , JAK3= Janus Kinase 3, NFKB2 = Nuclear Factor Kappa B 2, WAS= Wiskott Aldrich Syndrome, CGD= Chronic Granulomatous Disease, LAD 1= Leukocyte Adhesion Defect Type 1,HLH= Haemophagocytic Lymphohistiocytosis , GVHD = Graft versus Host Disease Adeno = Adenovirus, HHV6 = Human Herpes Virus 6, Varicella = Varicella zoster, EBV = Epstein Barr Virus

Data from the population-based Northern UK Region Young Persons' Malignant Disease Registry describe an age-standardized incidence rate of 121 per million per year in children aged 0-14 years diagnosed between 1968 and 1995, equating to 0.18% of children developing malignancy before their 15th birthday<sup>1</sup>. The latest UK incidence statistics indicate a similar risk of 0.2%<sup>2</sup>. A review of post-transplant secondary malignancies described its occurrence in up to 7% of recipients by 20 years post-transplant with no evidence of a plateau with longer follow-up<sup>3</sup>. Two large international registry-based studies describe the cumulative incidence of secondary solid malignancies in recipients of allogeneic HSCT for haematological conditions: using Kaplan-Meier analysis, invasive secondary solid malignancies (56% of which were not Post transplant lymphoproliferative disorders (PTLD)) occurred in 0.9%, 4.3% and 11% of 3182 children at 5, 10 and 15 years post-transplant<sup>4</sup>. More recently, using competing risks analysis, the cumulative incidence of secondary non-PTLD solid malignancies was 3.3% at 20 years post-transplant amongst 28,874 recipients of all ages<sup>5</sup>.

A European Bone Marrow Transplantation group survey estimated incidence of MDS/AML to be 1.2:1000 transplants, mostly occurring within 4 years of HSCT<sup>6</sup>.

## References

1. Cotterill SJ, Parker L, Malcolm AJ, Reid M, More L, Craft AW. Incidence and survival for cancer in children and young adults in the North of England, 1968-1995: a report from the Northern region Young Persons' Malignant disease registry. *British Journal of cancer*. 2000; 83 (3): 397-403
2. Available at: <http://www.cancerresearchuk.org/#heading-Zero-Children's> cancer statistics. Accessed 29<sup>th</sup> January 2018

3. Bomken S, Skinner R. Secondary Malignant Neoplasms Following Haematopoietic Stem Cell Transplantation in Childhood. *Children*. 2015;2: 146-173
4. Socie G, Curtis RE, Deeg J, Sobocinski KA, Filipovich AH, Travis LB et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukaemia. *Journal of Clinical Oncology*. 2000; 18 (2): 348-357
5. Rizzo JD, Curtis RE, Socie G, Sobocinski KA, Gilbert E, Landgren O et al. Solid cancers after allogeneic hematopoietic cell transplantation. *Blood* 2009; 113: 1175-1183
6. Hertenstein B, Hambach L, Bacigalupo A, Schmitz N, McCann S, Slavin S et al. Development of leukemia in donor cells after allogeneic stem cell transplantation—a survey of the European Group for Blood and Marrow Transplantation(EBMT). *Haematologica* 2005; 90(7): 969 – 975