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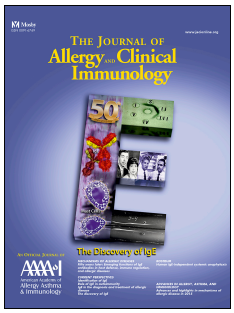

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Non-PTLD Malignancy post HSCT in patients with Primary Immunodeficiency: UK experience

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Short summary

Secondary malignancy post haematopoietic stem cell transplantation (HSCT) for malignant disorders is well recognized. There are very few published reports on malignancy post HSCT for Primary Immunodeficiency (PID). We report 12 cases of 944 patients, who developed non-PTLD malignancy post-HSCT for PID.

Key words

Primary Immunodeficiency; HSCT; non-PTLD malignancy

To the Editor

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

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

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

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

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

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

(P9,P12) .

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

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

P9 developed Acute Myeloid Leukemia (AML M4) 11 years post-HSCT which is uncommon. Unfortunately, it was undetermined whether leukemic cells were donor or recipient origin. 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 (See OR)[E6]. Multiple hit theory postulates that donor cells already acquired a first hit in the donor and additional hits are acquired in the host marrow microenvironment. Viral persistence, disturbed immunosurveillance and accelerated telomere shortening may also be contributory[6,7].

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

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

P7 had fungal granuloma pre-transplant, received voriconazole throughout transplant and developed actinic keratosis, a pre-malignant condition and later squamous cell carcinoma of the lower leg and auricular basal cell carcinoma. A retrospective study confirmed the association between voriconazole and the development of squamous cell carcinoma post-allogenic HSCT[9].

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

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

receiving myeloablative, reduced intensity or reduced toxicity conditioning and postulated that there may be synergistic effects of DNA damage from an alkylator added to fludarabine related inhibition of DNA repair used in reduced intensity or toxicity regimens[6].

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

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References :

1. Bomken S, Skinner R. Secondary Malignant Neoplasms Following Haematopoietic Stem Cell Transplantation in Childhood. Children. 2015;2: 146-173

2. McClain KL. Immunodeficiency states and related malignancies. Cancer Treat Res. 1997;92:39-61.

3. Kamani NR, Kumar S, Hassebroek A, Eapen M, LeRademacher J, Casper J et al. Malignancies after hematopoietic cell transplantation for primary immune deficiencies: a report from the Center for International Blood and

Marrow transplant Research. Biol Blood Marrow Transplant 2011; 17(12):1783-1789

4. Nelson AS, Vadjic CM, Ashton LJ , Marsney REL , Smith IN, Wilcox L et al. Incident cancers and late mortality in Australian children treated by allogeneic stem cell transplantation for non-malignant diseases. Pediatr Blood Cancer 2017; 64:197-202

5. Eapen M, Woo Ahn K, Orchard PJ, Cowan MJ, Davies SM , Fasth A et al. Long-term survival and late deaths after hematopoietic cell transplantation for primary immunodeficiency diseases and inborn errors of metabolism. BBMT 2012; 18:1438-1445

6. Shimoni A, Shem-Tov N, Chetrit A , Volchek Y, Tallis E, Avigdor A et al. Secondary malignancies after allogeneic stem-cell transplantation in the era of reduced-intensity conditioning; the incidence is not reduced. Leukemia 2013, *27*, 829–835

7. Wiseman DH, Donor cell leukemia : a review. Biol Blood Marrow Transplant 2011:17:771-789

8. Melnick M, Sedghizadeh PP, Allen CM, Jaskoll T. Human cytomegalovirus and mucoepidermoid carcinoma of salivary glands:Cell-specific localization of active viral and oncogenic signaling proteins is confirmatory of a causal relationship. Experimental and Molecular Pathology 2012;92(1):118-125

9. Wojenski DJ, Bartoo GT, Merten JA, Dierkhising RA, Barajas MR,El-Azhary

RA et al. Voriconazole exposure and the risk of cutaneous squamous cell carcinoma in allogenic hematopoietic stem cell transplant patients. Transplant Infectious Disease 2015 April : 17(2) : 250-258

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^2 F 150mg/m^2	MSD BM	100/0/0	Ph+ Pre B ALL	2.5	No	No	No	Died
2.MHC I systemic	13.6	F150mg/m^2 Mel140mg/m^2 Al 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^2 Mel140g/m^2 Al 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^2 F150mg/m^2 Al 0.3mg/kg	Matched UCB	100/97/93	Right Occipital Ewing Sarcoma	3.58	No	No	No	Alive
5.NFKB2 systemic	14	F150mg/m^2 Mel140mg/m^2 Al 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^2 Mel140mg/m^2 Al 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^2 Bu12.8mg/kg Al 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^2 Mel140mg/m^2 Al 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 umknown	1.0	Bu 12.8mg/kg Cy 200mg/kg Al 1mg/kg	MUD BM	96 Whole blood	AML	11	No	No	No	Alive
10.LAD1 systemic	1.4	F150mg/m^2 Mel140mg/m^2 Al 1mg/kg	MUD BM	100/100/100	Renal Cell Ca	11.2	No	Immune thrombo-cytopenia	No	Alive
11.T-B+NK+ SCID unknown	4.4	F 150mg/m^2 Mel 140mg/m^2 Al 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^2 F 150mg/m^2	MSD BM	0 whole blood	JMML	0.78	No	No	Adeno	Died

T = Treosulfan, F= Fludarabine, Al =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[1]. The latest UK incidence statistics indicate a similar risk of 0.2%[2]. 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[3]. 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[4]. 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[5].

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[6].

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 29th 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