Clinical and immunological outcome after paediatric stem cell transplantation in inborn errors of immunity

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Chapter 9

Malignancy post-haematopoietic stem cell transplant in patients with primary immunodeficiency

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Expert Review of Clinical Immunology 2020; 16(5); 493-511

Abstract

Introduction: Haematopoietic cell transplantation (HCT) is a curative treatment for an expanding number of primary immunodeficiencies (PIDs). Malignancies are more common in patients with PID than in the general population and this review will discuss whether or not a successful HCT is expected to abolish or alter this risk. Second malignancy post HCT for a malignant disease is well known to occur, but generally less expected in patients transplanted for PID.

Areas covered: This article reviews recently published literature focusing on the pattern of malignancy in children with PID, incidence and risk factors for developing malignancy post-HCT for PID and possible strategies to reduce the risks.

Expert opinion: Survival post HCT for PID has improved dramatically in the last 20 years and the genomic revolution has led to an expanding number of indications. To improve long-term quality of life attention needs to focus on late effects, including the possibility of malignancy occurring more frequently than expected in the general population, understand the risks and improve the process of transplantation in order to minimise them. Further studies are needed.

Introduction

Primary immunodeficiency (PID) or inborn errors of immunity (IEI) comprise a large, heterogeneous group of disorders, often due to single-gene mutations that result in defects in the development and function of the immune system. After the description of Bruton's agammaglobulinaemia by Colonel Odgen Bruton in 1952, more than 350 gene mutations associated with immunodeficiency disorders have been identified. (1-3) Recent studies have shown that PID is increasingly recognised with a prevalence of up to one in 1200 people worldwide potentially living with a PID (4-8). These disorders have diverse phenotypes including infection, malignancy, allergy, auto-immunity and autoinflammation. Although patients with PID commonly present with infection and immune dysregulation, malignancy occurs with a higher incidence and manifests earlier in life, than in the general population, with an overall relative risk varying from 1.4 to 5-fold in registry-based studies. (9-11) It can be the first presentation of PID in some patients. Lymphoproliferative disorders (LPD) represent 50% of all reported cancer in patients with PID. After infections, malignancy is the second most common cause of death in patients with PID. (3, 12)

Advances in haematopoietic cell transplantation (HCT) and supportive care have resulted in significant improvements in survival for children with PID. Following the first successful HCTs for a child with severe combined immunodeficiency (SCID) and another for Wiskott-Aldrich syndrome (WAS) in 1968, transplant survival and graft outcomes have significantly improved in the modern era due to many factors: superior HLA matching technology, greater availability of alternative donors, graft engineering, additional cellular therapy, reduced toxicity conditioning regimens, pharmacokinetic-guided conditioning regimens, vigilant infection surveillance with more effective antimicrobial therapy and better supportive care and treatment for complications. These new developments enable precise personalised transplant care including patient-tailored conditioning regimens and precise prescription of graft components. (13-16) Over the last several decades, the number of HCTs performed for PID has increased and more than 2500 children have received HCTs for PID in Europe and North America. (17, 18) Transplant survival has improved to 90% for SCID with a matched family donor and 70% with a matched unrelated donor transplant. (19, 20) Similar transplant survival has been reported in non-SCID PID recently. (21, 22) Younger age at transplant has been consistently shown to be a significant positive predictor of transplant outcome. (21, 23). In addition, precise molecular diagnosis and understanding of the natural history of PID enable early identification of suitable candidates for HCT. In many patients with non-SCID PID, HCT has developed from being a last resort into the standard of care that corrects the defects in immunity.

Secondary malignancies are a well-known complication of conventional chemotherapy and radiation treatment for patients with various primary cancers and are also well-recognised as a complication among transplant survivors. Malignancy post-HCT (MPT) for haematological disorders has been reported since 1970 and several large studies have shown adult and paediatric transplant survivors are at high risk of MPT with reported incidences of up to 10-15% by 15 years post-HCT. More recent studies using competing risk analysis have shown a lower magnitude of risk of 3-7%. MPT has been reported in both autologous and allogeneic HCT recipients in children. (24-27). MPT has been described after HCT for aplastic anaemia, haemoglobinopathy and inborn errors of metabolism. For MPT for aplastic anaemia, the largest experience was reported by EBMT which included 748 patients who underwent HCT and 860 patients who were treated with immunosuppressive therapy (IST). Patients who developed haematological malignancies within 6 months or solid tumours within 12 months were excluded as these cancers might be due to the underlying diagnosis rather than therapy. The 10-year CIN of second cancer was 3.1% with HCT and 18.8% with IST. The risk of solid cancers was the same in the two groups but the pattern of tumours was different, primarily solid cancers after HCT and haematological malignancies after IST. The major risk factors for MPT were increasing age at HCT and the use of radiation therapy in the conditioning regimen. Deeg HJ *et al*. reported the risk of MPT for 700 patients who underwent HCT for aplastic anaemia or Fanconi anaemia. The risk of MPT at 20 years post-HCT was 14% for the entire cohort, rising to 42% in 79 patients with Fanconi anaemia. There were 18 solid MPT (all squamous cell carcinoma except one) and 5 haematological MPT. Radiation and use of azathioprine for chronic GvHD were the risk factors of MPT.(28) Although MPT has been described in haemoglobinopathies and inborn errors of metabolism, it is unclear if the risk is increased compared to the general population.

There is also an increased risk of a wide range of cancers associated with solid organ transplantation. The most extensive data come from a cohort study that analyzed the frequency of malignancy in over 175,000 solid organ transplant recipients between 1987 and 2008. (29)The most common organs transplanted included kidney, liver, heart, and lung (in 58, 22, 10, and 4 percent of cases, respectively). Malignancy was identified in over 10,656 cases, which correlated with a standardized incidence ratio (SIR) of 2.10 (95% CI 2.06-2.14) compared with the general population and an excess absolute risk (EAR) of 719 cases per 100,000 person-years. Malignancy occurred in more than 30 different primary sites, but those with a fivefold or greater increase, compared with the general population, included Kaposi sarcoma, skin, Non-Hodgkin lymphoma, liver, anus, vulva and lip.

Whilst allogeneic HCT corrects the underlying immune defect preventing recurrent life-threatening infection, achieving immune competence post-HCT has been hypothesized to

reduce the risk of malignancy in patients with PID. However, HCT may not eradicate the risk of malignancy completely. As transplant survival has improved, the number and length of follow-up of survivors after successful HCT is increasing. With these increases, it is now known that malignancy post-HCT may occur, causing significant morbidity including late and premature death in transplant survivors. This review will focus on the pattern of malignancy in children with PID, incidence and spectrum of malignancy in post-HCT for PID, proposed mechanism and risk factors for carcinogenesis in post-HCT for PID, proposed strategy to reduce the risk of MPT, how to identify patients at risk and how to manage these patients.

Pattern of Malignancy in Primary Immunodeficiency

It has been estimated that the overall risk of developing cancer in patients with PID ranges from 4 to 25% (table 1). (12, 30) In 2018, the United States Immune Deficiency Network (USIDNET) published the largest study which included 3658 PID patients who enrolled in the registry between 2003 and 2015. This registry study observed a 1.42-fold excess relative risk of cancer in patients with PID compared to the age-adjusted population. The greatest increase in cancer incidence was observed in lymphomas in both males (10-fold excess relative risk) and females (8-fold excess related risk). This excessive lymphoma risk was seen in patients with common variable immunodeficiency (CVID) which was the most common PID in the registry. Overall, males with PID had a 1.91-fold excess relative risk of cancer while females with PID had similar cancer rates compared to their age-adjusted population. There was no significant difference in the incidence of common cancers (lung, colon, breast and prostate) in patients with PID compared to the general population. (3) The Australian Society of Clinical Immunology and Allergy registry data which involved 1132 subjects showed that the SIR was significantly elevated for all cancer (SIR 1.6), cancer of the thymus gland (SIR 67.3), non-Hodgkin lymphoma (SIR 8.82), stomach cancer (SIR 6.10) and leukaemia (SIR 5.36) (31) The Netherlands reported 10% of cancer in 745 PID patients in the Dutch national registry between 2009 and 2012. Compared to the general Dutch population, PID patients had a 2.3-fold excess risk of developing cancer, and more than 10-fold increased risk for some solid tumours (thymus, endocrine organs) and haematological malignancies (leukaemia and lymphoma). (10)

Disorders which are associated with a higher incidence of cancer are CVID and ataxia telangiectasia which account for 30% and 24% of reported cancer among PID patients respectively. Approximately 30% of cases are reported in association with Wiskott Aldrich syndrome, severe combined immunodeficiency and selective IgG deficiency. (32, 33) The Immunodeficiency Cancer Registry database on immunodeficiency-associated cancer at the

University of Minnesota showed that nearly 60% of all reported malignancies in PID were lymphomas, 85% of which were non-Hodgkin lymphoma (34). An USIDNET study also showed that lymphomas were the most common cancer and accounted for 48% of all cancers in PID patients, followed by skin cancer (15%) and gastrointestinal (8%) and genitourinary cancers (8%). (3) Patients with PID develop lymphomas at younger ages compared to the general population. Cancers of all types in PID patients are likely to be disseminated at the time of diagnosis. Non-Hodgkin lymphomas in these patients are likely to be of B cell origin, be associated with EBV infection, of high histological grades and involve extranodal tissues, particularly the gut and central nervous system.

Although patients with PID are well-known to be at significant risk of developing malignancy, our understanding about the exact mechanisms of carcinogenesis in PID remains incomplete. One of the functions of the immune system is to recognise and destroy cancer cells without causing toxicity to normal tissues and to prevent cancer recurrence by long-term memory. Similar to the aetiology of cancer in childhood, carcinogenesis in children with PID is multi-factorial (figure 1). The proposed mechanisms of increased risk of malignancy in PID encompass reduced immune surveillance, dysregulation of haematopoiesis and impaired DNA damage responses. (35) These can be classified into intrinsic factors and extrinsic factors. Intrinsic factors are mainly associated with haematological malignancies and encompasses impaired genetic stability (e.g. defective DNA repair such as ataxia telangiectasia, Nijmegen Breakage syndrome), genetic predisposition (e.g. leukocyte development defects such as severe congenital neutropenia and bone marrow failure syndrome, defective tumour suppression genes such as DOCK8 deficiency, CVID and autoimmune lymphoproliferative syndrome), and impaired immune function (e.g. X-linked lymphoproliferative disease, ITK deficiency, CD40 ligand deficiency). Extrinsic factors are commonly associated with carcinomas and include impaired clearance of oncogenic viruses (e.g. Epstein-Barr virus in XMEN disease, human papillomavirus in WHIM syndrome), chronic tissue inflammation and iatrogenic (e.g. radiation). Interplay between these factors and impaired immunosurveillance render PID patients at higher risk of developing cancers. (36, 37)

Incidence and spectrum of malignancy in transplant survivors of primary immunodeficiency

Whilst there are a number of single centre and multi-centre studies which reported MPT in children with haematological disorders (24, 38-46), there have been limited studies on MPT in children with PID (Table 2 and 3). The reported incidences of MPT in PID transplant survivors are 2.3% by Kamani *et al*., 1.5% by Nelson *et al*. (non-malignant HCT, including PID) and 1.3%

of non-PTLD MPT by Unni *et al*. In Nelson's report, there were 6 malignancies in 318 patients who underwent allogeneic HCT for non-malignant disorders. The cumulative incidence of malignancy was 0.3 ± 0.3% and 2.3 ± 1.2% at 5 years and 10 years post-HCT respectively. This study showed that 15 times more malignancies occurred after HCT in the study population than expected in the age- and gender-matched Australian general population. In this cohort, one hundred and thirty patients had PID: a patient with SCID and another with CGD developed solid tumours but there was no further information documented. (47) Unni *et al.* carried out a retrospective study of 944 patients with PID who underwent HSCT in 2 specialised centres in the UK. Twelve patients (1.27%) developed non-PTLD malignancy at a median of 3.75 years (range 3 months to 11.2 years) post-HCT. (48) No patients received radiotherapy but all received chemotherapy with at least 1 alkylating agent for conditioning prior to HCT.

Spectrum of malignancy post haematopoietic cell transplantation

MPT is conventionally classified into three distinct groups: 1) lymphoma, including post-transplant lymphoproliferative disease (PTLD) 2) myelodysplasia (MDS) and acute myeloid leukaemia (AML) 3) solid tumours. The time course for developing MPT is variable. Leukaemia and lymphomas develop relatively early post-HCT whereas solid tumours have a longer latency period and are being increasingly reported because of improved transplant survival and longer follow-up. In 2003, Baker *et al.* reported multiple MPT in 8 (5.6%) of 137 patients who developed MPT after allogeneic HCT for various indications in Minnesota, including PID. All were solid MPT expect two who had AML/MDS. The first MPT was diagnosed at a median of 3.9 years post-HCT and the second MPT was diagnosed at a median of 6.3 years post-HCT. Three of these patients had recurrence of skin cancer and the remaining 5 patients had developed two distinct new cancers. (49) In 2019, Baker *et al.* published another large series from Seattle which showed that cumulative incidence of MPS by 30 years after HCT was 22%(50)

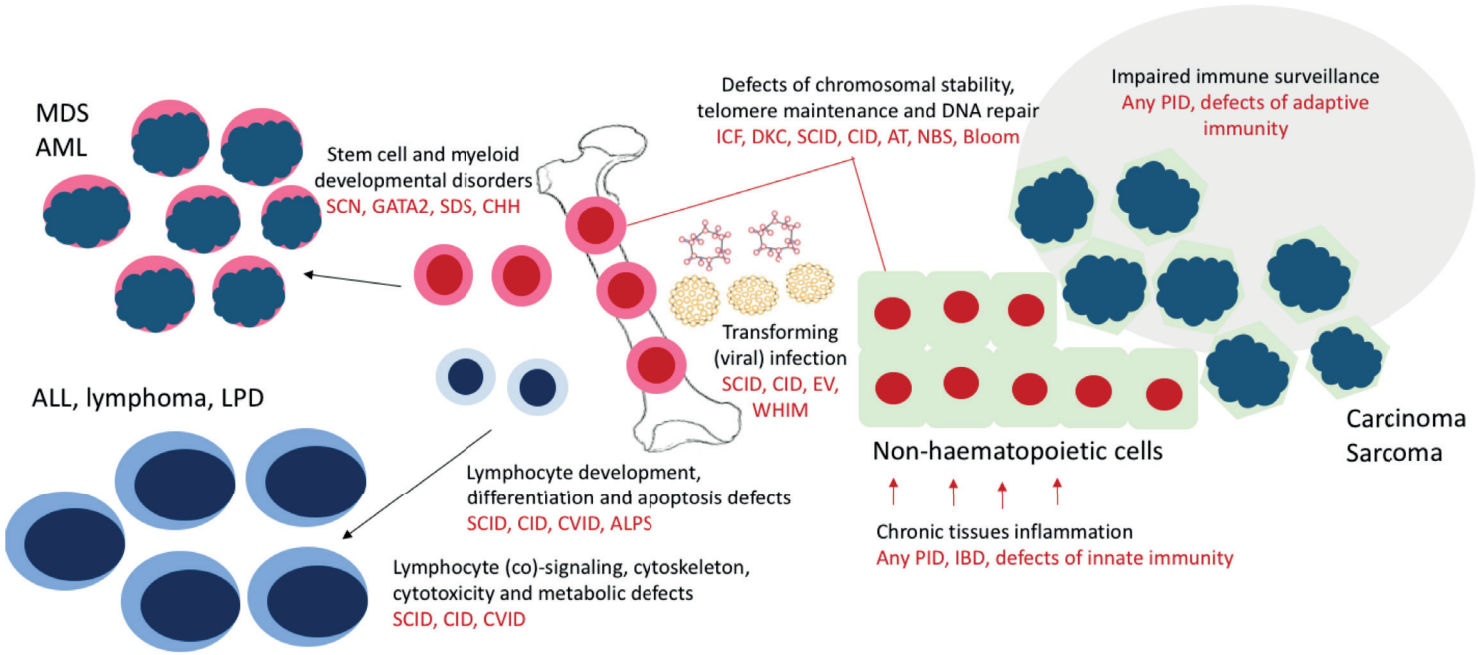

Figure 1: Proposed mechanism of carcinogenesis in patients with primary immunodeficiency

Post-transplant lymphoproliferative disease

PTLD is the most common MPT in the first year after HCT and solid organ transplantation. Most of these cases are related to impaired immune function during early post-HCT and in most cases, proliferation of EBV infection. CIBMTR and the Fred Hutchinson Cancer Research Centre reviewed the largest experience of PTLD in adult and paediatric cohorts which included 26901 allogeneic HCT survivors. This analysis excluded PID (n=532, 20 PTLD, 8.6%) and Fanconi aneamia (n=328, 1 PTLD, 0.3%). In this study, 127 PTLD were identified and the observed to expected ratio was 29.7% (95% CI, 24.7 to 35.2) compared to age-, sex- and country-adjusted population. The risk factors for PTLD were T-cell depletion (RR 3.1-9.4), use of ATG (RR 3.8), HLA mismatched in the presence of T-cell depletion/ATG (RR 3.8), acute (RR 1.7) and chronic (RR 2.0) GvHD. Lower risks were found for T-cell depletion methods that remove both T and B cells. This analysis demonstrated a multiplicative effect of multiple risk factors on incidence; the incidence was low (0.2%) in 21686 patients with no major risk factors, but increased to 1.1%, 3.6% and 8.1% with 1, 2 or ≥3 major risk factors. (45)Kamani *et al.* reported 52 post HSCT malignancies in a large study of 2266 patients with PID giving an overall incidence of 2.3%. The most frequent malignancy was early-onset PTLD in 45 cases, which was associated with T cell depleted grafts. (51, 52)

Therapy-related acute myeloid leukaemia and myelodysplasia

In Nelson's report, 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: a patient with Omenn's syndrome developed a desmoplastic squamous cell carcinoma 170 months after unrelated donor HSCT, a patient with combined immunodeficiency (CID) developed hepatocellular carcinoma 84 months after unrelated donor HCT and another patient developed a brain tumour after HCT for SCID. The incidence of non-PTLD malignancy was 0.3%.(47)

Solid malignancy post-transplant

A wide spectrum of solid MPT has been described and the incidence of solid MPT has been reported to rise over time and successive studies with follow-up to 20 years not showing a plateau in their occurrence (27, 52, 53). Overall, the reported cumulative incidence of solid MPT ranges from 1.2 to 1.6% at 5 years, from 2.2 to 6.1% at 10 years and from 3.8 to 14.9% at 15 years post-HCT. In the CIBMTR report, HCT survivors developed new solid malignancies at twice the expected rate compared to the general population (observed-to-expected ratio 2.1; 95% CI 1.8-2.5). The cumulative incidence of new solid MPT was 1% at 10 years, 2.2% at 15 years and 3.3% at 20 years post-HCT. (27) Similar results were reported by Kolb *et*

al. which included 1036 patients who were transplanted for malignancy, severe aplastic anaemia, PID and inborn errors of metabolism. Socie *et al* reported that solid MPT risk after HCT for childhood cancer increased over time to an estimated 11% at 15 years post-HCT and that age at HCT less than 10 years of age and high dose TBI are associated with higher risk of solid MPT. (24) Unni *et al.* carried out a retrospective study of 944 patients with PID who underwent HSCT in 2 specialised centres in the UK. Twelve patients (1.27%) developed non-PTLD malignancy at a median of 3.75 years (range 3 months to 11.2 years) post-HCT. (48) Overall, the reported cumulative incidence of solid MPT ranges from 1.2 to 1.6% at 5 years, from 2.2 to 6.1% at 10 years and from 3.8 to 14.9% at 15 years post-HCT.

All types of solid cancer have been described in HCT survivors and the types of cancer reported more frequently in HCT survivors include, melanoma, cancers of the oral cavity and salivary glands, brain, thyroid, uterine cervix, breast, bone and connective tissue. Squamous cell carcinoma (SCC) of the oral cavity is more common in HCT survivors, particularly among those with chronic GvHD, Fanconi anaemia, and prior chronic lichenoid lesions of the oral mucosa.

Proposed mechanism and risk factors of carcinogenesis in PID transplant survivors

The risk of developing MPT varies greatly among studies and is dependent on patient-, disease- and transplant-specific factors, including primary disease, age at HCT, chemotherapy agents, radiation dose and field, length and severity of immunodeficiency, graft-versus-host disease, infection and lifestyle (figure 2). PID transplant survivors represent a unique cohort compared to transplant survivors of malignancy. PID patients have an inherent risk of malignancy. Most PID patients do not receive pre-transplant chemotherapy and radiation is rarely used as conditioning regimen. Increased susceptibility to infection and extent of donor chimerism may play a role in patients with PIDs developing MPT.

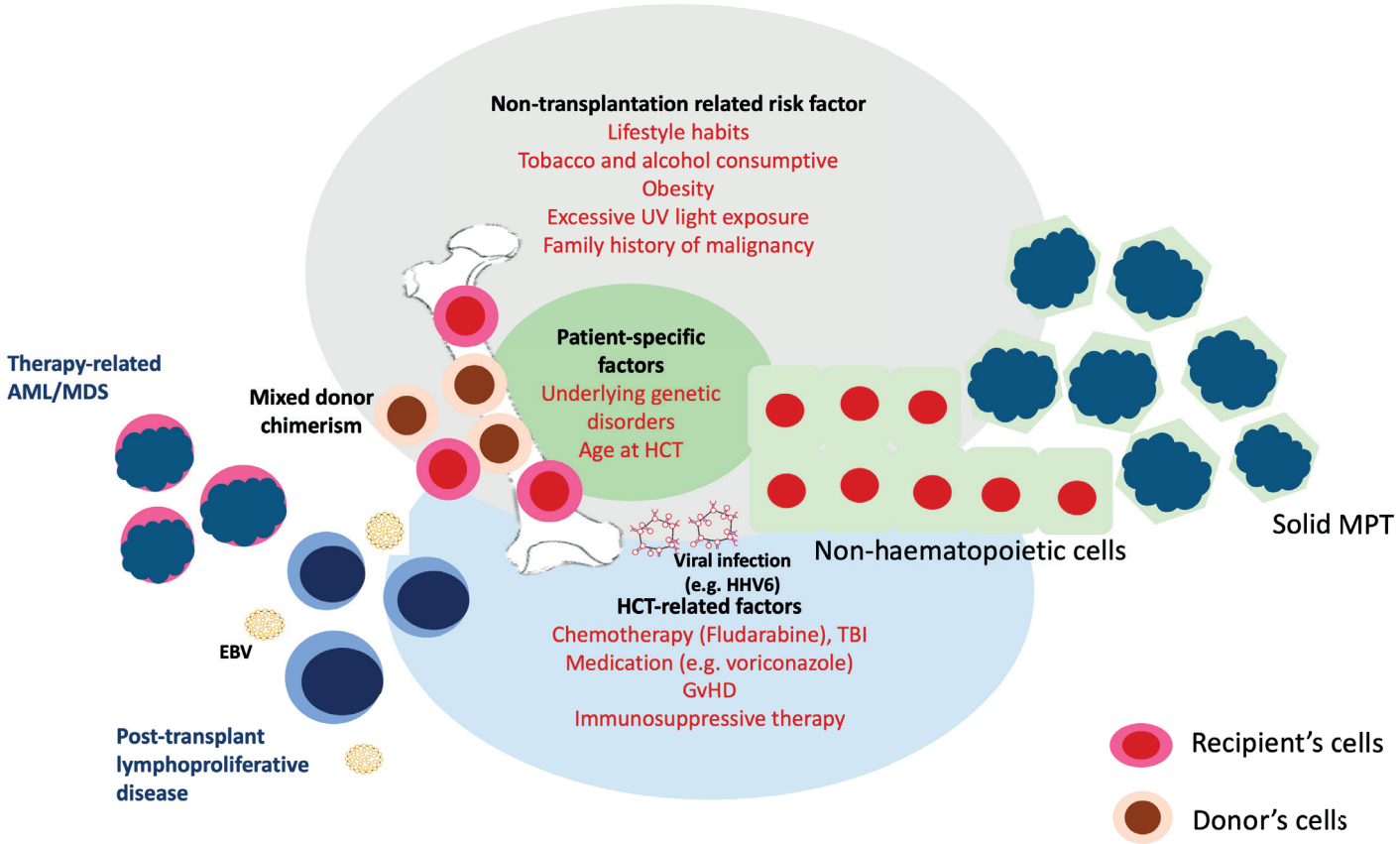

Figure 2: Proposed mechanism of carcinogenesis after HCT in patients with primary immunodeficiency

Patient-specific risk factors: Primary disease and age at transplant

Laffort *et al.* first described 9 patients with IL-2Ry- and JAK3-deficient SCID with extensive cutaneous human papillomavirus-associated warts. (54) The median onset was 8 years post-HCT (range 3-15 years). Subsequently Kamili *et al*. reported a further 6 affected patients. (55) The warts are resistant to conventional treatments and may pose a risk of malignant transformation. (56) The occurrence of these warts is not clearly associated with degree of donor chimerism or the level of T-lymphocyte reconstitution post-HCT, but may be associated with low numbers of NK cells or possibly poor NK cell function. Abd Hamid *et al*. reported 7 of 31 long-term survivors with IL-2Ry- and JAK3-deficient SCID to have extensive warts and in this study there was no difference in the mean values of NK cells at last follow up between those with or without warts or between conditioned and unconditioned recipients.(57) Although the pathophysiologic mechanism is not completely understood, evidence has been provided that lack of the common γ chain function in cells such as keratinocytes may impair the secretion of chemokines that may guide the influx of protective immune cells. Therefore changing the cells in the haematopoietic system by HSCT or gene therapy which does not alter cells out-with the haematopoietic system leaves these patients at risk of developing HPV- associated warts and vigilance is required to monitor for any malignant transformation. Most centres would recommend HPV vaccination for these patients and further studies are needed to see if this will reduce the incidence.

Kesserwan *et al.* reported an association between Dermatofibrosarcoma protuberans (DFSP) and ADA deficient SCID patients. DFSP is normally a particularly rare malignant skin tumour in childhood with a low risk of metastasis.(58) The characteristic histologic finding is a spindle cell tumour with a storiform pattern which is CD34+. At the cytogenetic level it is associated with a characteristic chromosomal translocation (t[17;22] [q22;q13]) resulting in the COL1A1-platelet-derived growth factor β (PDGFB) fusion gene. Kesserwan *et al.* described 8 patients with DFSP lesions. Mostly these presented as multiple small brown atrophic plaques, less than 1cm in diameter which had been present in some cases since birth. Cases have been reported post treatment with PEG-ADA and HSCT suggesting that despite immunological correction of the underlying disorder this association remains a risk. (58-60) Toxic metabolites in the skin and an increased propensity for DNA strand breaks in patients with ADA deficiency may be involved as mechanisms for this association. Careful histological and cytogenetic testing of lesions is required to make the diagnosis and treatment requires wide excision with margin control due to the infiltrative nature of the lesions.

The impact of age of risk factor of MPT has been studied in a number of large registry studies in HCT for malignancy. CIBMTR assembled a cohort of 1487 paediatric HCT and showed that

younger age (<10 years) at allogeneic HCT was associated with greater risk of MPT, especially brain and thyroid tumours (RR 3.7) but had no effect on autologous HCT. (24, 25) There is no study to analyse age at HCT in patients with PID.

Transplantation-related risk factors

Chemotherapy

Many studies have shown that patients who have been treated with chemotherapy and/or radiotherapy followed by HCT have an increased risk of developing secondary cancer. However, MPT has also been reported in patients who only received chemotherapy alone for HCT. In animal models, a higher incidence of secondary cancer was also found in dogs that were given DLA-identical marrow from a litter mate after TBI than in controls dogs or dogs given only chemotherapy for conditioning.

In PID patients with increased susceptibility to cancer, use of chemotherapy particularly alkylating agents induce DNA breakage which may predispose to malignant transformation. In recent years the use of reduced intensity and reduced toxicity conditioning has increased which may reduce the risk of malignancy post-HSCT.

In Unni *et al.*'s study no patients received radiotherapy but all received chemotherapy with at least 1 alkylating agent for conditioning prior to HCT (25).

Fludarabine-based conditioning, moderate-severe chronic GVHD and chronic myeloproliferative or non-malignant disease were shown to be risk factors for second malignancy in adult patients.(61, 62). 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. (62)

Medication

Voriconazole is commonly used in patients with PID pre- and post-HSCT. A report documented an association between voriconazole and the development of squamous cell carcinoma post-allogenic HSCT.(63) A patient in Unni *et al.*'s study with XL-CGD had fungal granuloma pre-transplant, received voriconazole throughout transplant and developed actinic keratosis, followed by squamous cell carcinoma of the lower leg and an auricular basal cell carcinoma.

Graft versus host disease and viral infection

In Unni's study 2 patients who both had oral cGVHD and prolonged HHV6 viraemia post-HCT developed a parotid muco-epidermoid carcinoma (MEC) at 6 and 3 years post-HSCT. There are data which link parotid MEC to prolonged CMV infection, which can remain dormant in the salivary glands and so the presence of HHV6 in a patient with an immature immune system may play a role. Two additional patients had GVHD which together with prolonged immunosuppressive treatment may alter the microenvironment and depress normal tumour immune surveillance. (64)

Donor chimerism

In Unni *et al*.'s study, two patients lost donor engraftment in whole blood or B- cell and myeloid cell lineages before the onset of Philadelphia positive acute lymphoblastic leukemia in one and juvenile myelomonocytic leukemia in another. Both malignancies were confirmed to be recipient in origin. The first patient had RAG 2 deficiency and the second Griscelli syndrome, both of which predispose to malignancy. Alternatively, recipient stem cells surviving chemotherapy may have acquired genotoxic insults. Therefore the question arises that if they had had full donor chimerism this may not have happened.

Non-transplantation related risk factors

As for the general population lifestyle habits are important risk factors for the development of malignancies. Tobacco and alcohol consumption, obesity, excessive UV light exposure and a family history of malignancy may increase the risks.

Strategy to minimise risks of malignancy post haemato-poietic cell transplantation

Optimising transplant related factors

Outcomes of transplant for PIDs have improved dramatically over the last 20 years due to multiple factors. Moving towards low intensity rather than highly toxic traditionally used myeloablative regimens has led to less toxicity both in the short-and long-term.

Whilst moving away from toxic alkylating agents may decrease the risk of malignancy, an increase in mixed chimerism may leave the patient with recipient cells with a predisposition to malignancy depending on the underlying disorder and therefore choosing the best conditioning regimens remains a balancing act. A personalized approach to each patient with the ability to use pharmacokinetic monitoring of conditioning agents and blood levels of

serotherapy drugs will enable physicians to maximise the chance of donor engraftment with good levels of donor chimerism and immune reconstitution whilst minimising short- and long-term toxicities. (65-68)

The ability of certain antibodies to open up the haematopoietic stem cell niche is an exciting prospect which may allow conditioning in the future without the need for toxic chemotherapy. CD45 is selectively expressed on all leucocytes and haemopoietic progenitors, but is absent on non-haemopoietic tissues. Straathoff and colleagues reported 16 patients with PID who were less than one year of age or had significant pre-existing co-morbidities. The conditioning regimen comprised alemtuzumab 0·2 mg/kg daily for 3 days for unrelated donors, or 0·1 mg/kg daily for matched sibling donors on day –8 to day –6, clinical grade rat anti-CD45 (YTH 24·5 and 54·12) 0·4mg/kg on day –5 to day –2, fludarabine (30 mg/m^2 daily for 5 days on day –8 to day –4) and cyclophosphamide (300 mg/m^2 daily for 4 days on day –7 to day –4). Twelve patients were alive and well at the end of the study, one failed to engraft and was successfully re-transplanted and 3 died – none of conditioning toxicity. Donor chimerism was variable but high level and sufficient to cure disease in the survivors. (69)

A clinical trial is currently in progress using anti-CD117 antibody to treat patients with primary immunodeficiencies (AMG191 Conditioning/CD34+CD90 Stem Cell Transplant Study for SCID Patients, ClinicalTrials.gov Identifier: NCT02963064). This antibody to CD117 (otherwise known as c-kit receptor) selectively depletes haematopoietic stem cells. (70) Early results of this dose finding study reported that some donor stem cell chimerism, leading to donor T- and B-lymphocyte chimerism can be achieved.(71)

The level of donor chimerism is not just related to the conditioning regimen but also to factors such as stem cell dose in the transplant product. Good results have been obtained with well-matched donors using peripheral blood stem cells which lead to a higher stem cell dose than traditionally used bone marrow, without an increase in significant graft versus host disease when alemtuzumab is used.(72)

Other ways to improve chimerism post-transplant include the use of additional cells as an add-back either in the form of stem cells or T cell lymphocytes.

GVHD

Improved methods of HLA typing mean that better matched donors are now being used which decreases the risk of GVHD. In addition, timing and dosing of serotherapy used in the conditioning regimen are critical for the prevention of GVHD but need to be balanced against the impact on time to immune reconstitution particularly in the setting of PID with viral infections. Biomarkers to detect patients at risk of GVHD may become part of routine

practice enabling patient specific preventive strategies. If GVHD occurs prompt treatment is important. Methods such as Extracorporeal photopheresis (ECP) are now widely available which will improve previously poor outcomes of patients with steroid-resistant acute and chronic GvHD.(73) All these aspects will limit the impact of GVHD on carcinogenesis.

Optimizing non-transplant-related factors

Giving patients advice on lifestyle choices and avoiding high risk behaviours such as smoking and sun-bathing is important for minimising the risk of malignancy.

Surveillance for MPT in PID transplant survivors

All patients who undergo HCT for PID should have long-term follow up. Once they become adults, transition to adult services is very important. Patients should be counselled regarding the possible risk of malignancy and in addition to specific follow up according to their underlying diagnosis, type of HCT and any complications, should take part in routine screening for the general population together with encouraging self-examination.

Treatment of MPT in patients with underlying PID

There is no data about specific treatment of various malignancies post-transplant in patients with PID and so conventional treatment of the malignancy is recommended.

Conclusion

Second malignancy post HCT for a malignant disease is well known and well-established long-term follow up recommendations include surveillance for secondary malignancies. The occurrence of malignancy in patients with PID is known to be higher than in the general population, but the risk of malignancy post HCT in this group of patients is less well known. In theory if the underlying defect which may predispose to malignancy is only in the haematopoietic cells and the defect is cured, the risk of malignancy should be reduced. However, many PIDs, such as DNA repair defects, have features outside the haematopoietic cells which may therefore still pose a risk of developing disease-related malignancies. Incomplete donor chimerism post HCT may leave a patient at risk of malignancies in affected haematopoietic cell lines that are not completely corrected. In addition, the procedure of the transplant itself including use of alkylating agents and risk of complications such as GVHD and viral infection may increase risks of malignancy occurring. Therefore, it is important to look for malignancies as part of long-term follow up for patients post HCT for PID.

Expert Opinion and future perspectives

HCT is a curative treatment for an increasing number of PIDs. Survival after transplant has improved enormously in the last 20 years. Good quality of life with long-term healthy immune reconstitution and minimal late effects is therefore the goal. A systemic review or meta-analysis of existing data would be helpful to definite the risk factors of MPT.

Large scale, long-term follow-up of PID transplant survivors is required, including surveillance for malignancies, to improve our understanding of the spectrum of malignancies, better define the risks and therefore improve the way we perform HCT to minimise these risks. Multi-centre studies are needed.

A personalised approach to transplant will become more common. Biomarkers to identify patients at risk of developing malignancy may become available in order to allow tailoring of the approach to HCT and post HCT surveillance. PK monitoring with targeted dosing of chemotherapeutic agents and measuring levels of serotherapy used for conditioning, together with precise cell dosing in grafts, are becoming more common and in 5 years' time may become routine practise. Reduced toxicity conditioning will continue to evolve, for example using antibodies to open up the stem cell niche and thus avoid the use of DNA damaging alkylators which may have an effect on tissues out with haematopoietic cells.

Strategies to prevent and treat GVHD which has a role in carcinogenesis will continue to improve. For example, in our own centre the choice of donor for a patient with severe combined immunodeficiency if they do not have a matched sibling donor is a haploidentical parent using CD3+ alpha beta depletion together with CD19+ depletion to prevent GVHD and post-HCT LPD. (74, 75) Studies are ongoing using alternative techniques for haploidentical transplants including the use of post HCT cyclophosphamide, CD45RA depletion which retains the CD45RO-bearing T lymphocytes which are more likely to confer antiviral activity, giving additional caspase gene modified T cells which can be switched off if GVHD occurs, or CD45RA depleted cells post-HCT to improve immune reconstitution. (76-79) It may be that these techniques will supercede the use of unrelated donors, with their higher risk of causing GVHD, for all patients with PID.

Monitoring for infection and pre-emptive treatment will continue to improve. The use of T lymphocytes directed against specific viral epitopes will become more widely available. These can be either donor-derived or from third party banks. (80, 81) This will minimise the risks of carcinogenesis caused by viral infections such as CMV.

Finally, international standards for follow up of patients post HCT for PID should be developed which include surveillance for both disease-specific and other forms of malignancy which occur.

Table 1 Reported malignancies in PID patients from registry studies

Author Year	Ref	Year	Study cohort	Median age at dx of PID (range)	No. of patients with malignancy	Median age at diagnosis of malignancy (range)	Primary diagnosis of patients with malignancy	Type of cancer	Remarks
Mayor 2018 United States Immune Deficiency Network (USIDNET)	[3]	2003-2015	3658 35% CVIDD 13% CGD 12% DiGeorge syndrome 7% SCID 7% WAS 4% HyperIgM syndrome 23% others	NA	171 (4.9%)	NA	119 (70%) CVID 13 (9%) hypogammaglobulinemia and agammaglobulinemia 8 (4.6%) WAS 4 SCID 3 ataxia telangiectasia 3 hyperIgE STAT3 2 cartilage hair hypoplasia 1 DOCK8 1 Activated PI3K delta 1 CID 16 others	82 (48%) lymphoma 25 (15%) skin cancers 14 (8%) genitourinary 14 (8%) gastrointestinal cancers 10 (6%) breast cancer 9 (5%) endocrine cancers 6 (4%) head and neck cancers 5 (3%) lung cancers 2 (1%) bone cancers 4 (2%) unspecified	1.42-fold excess relative risk compared with the age-adjusted population Male PID: 1.91 excess relative risk Female PID: no excess risk Male PID: 10-fold increase for lymphoma Female PID: 8.34-fold increase for lymphoma

Author Year	Ref	Year	Study cohort	Median age at dx of PID (range)	No. of patients with malignancy	Median age at diagnosis of malignancy (range)	Primary diagnosis of patients with malignancy	Type of cancer	Remarks
Jonk-man-Berk 2015 Nether-lands	[10]	2009-2012	745 687 (92.9%) alive and 58 (7.8%) died before the study analysis 1118 had HCT (38 died) 61% predominantly antibody disorders 11% phagocytic disorders 9% other well-de-fined PID 8% predominantly T cell deficiencies 4% Autoimmune and immune dys-regulation 4% unclassified im-munodeficiencies 2% complement deficiencies 1% defects in innate immunity	8.0 years (range, 0 – 80 years)	60 (8.1%)	43.0 years (range, 3.0 -77.0)	44 (73.3%) hypogammaglobulinemia (28 CVID)	3 leukaemia 17 lymphomas (14 NHL, 3 HD) 40 (66.7%) solid cancers 14 skin (13 SCC) 6 gastrointestinal tumours 5 breast 4 endocrine 3 lung 2 thymus 2 genital male 2 bladder 1 bone 1 pancreas	PID had an overall 2.3-fold increase in the life time chance of developing a malignancy compared to general population in Netherlands

Author Year	Ref	Year	Study cohort	Median age at dx of PID (range)	No. of patients with malignancy	Median age at diagnosis of malignancy (range)	Primary diagnosis of patients with malignancy	Type of cancer	Remarks
Vajdic 2010 Australia	[31]	1990-2008 Mean duration of FU: 16 years (SD 5.4 years)	1132 78% predominately antibody deficiency 7% complement deficiency 4.8% Combined T and B cell immunodeficiency 5.8% other well-defined immunodeficiency syndromes 3.5% congenital defects of phagocyte number 1.2% diseases of immune dysregulation	Median age at registration: 25 years (range, 0 – 95 years)	58 (5.7%) 55 first cancer 3 second primary cancer	NA	53 predominantly antibody deficiencies	55 first cancer 3 second cancer 16 NHL 1 HD 4 leukaemia 3 stomach 2 thymus 1 adrenal 1 thyroid 3 prostate 3 bladder 1 ovary 12 breast 4 melanoma 2 trachea, bronchus, lung 1 pancreas 4 colon	Standardized incidence ratio all cancers: 1.6 thymus: 67.3 NHL: 8.82 stomach: 6.10 leukaemia: 5.36

CGD: chronic granulomatous disease; CID: combined immunodeficiency; CVID: combined variable immunodeficiency; FU: follow-up; HCT: haematopoietic cell transplantation; HD: Hodgkin's lymphoma; NA: not available; NHL: non-Hodgkin's lymphoma; PID: primary immunodeficiency; Ref: reference; SCID: severe combined immunodeficiency; SCC: squamous cell carcinoma; WAS: Wiskott-Aldrich syndrome

Table 2 Reported malignancy post allogeneic haematopoietic stem cell transplant in children with haematological disorders

Author Year	Ref	Year of HCT/ duration of FU	Study cohort	Age at HCT	No of MPT	Primary diagnosis of patients who developed MPT	Type of cancer	Interval between HCT to MPT	Donor for patients who developed MPT	Conditioning for patients who developed MPT	Outcome of patients with MPT	Remarks
Baker 2019 Single centre, Seattle	[50]	1969-2014 Median duration FU (living): 12.5 years (range, 1.0 to 42 years)	4905 (excluded Fanconi anaemia, n = 20 and non-haematological solid tumour, n=140) 4500 haematological malignancy 405 non-malignant diseases (AA, PID, HLH, haemoglobinopathy and others)	Adult and paediatric cohorts Median: 34.5 years (range, 0.3 – 78.9 years)	499 (11%) MPT (excluded SCC and BCC of skin) 81 had multiple MPT (69 had 3 MPT, 9 had 3 and 3 had 4)	NA	NA	Median 10.3 years (range 1.0 to 39.7 years)	NA	NA		CI of MPT: 22% at 30 years post-HCT Highest incidence of MPT was in survivors exposed to unfractionated (600-100cGy) or high dose fractionated (14.4 to 17.5Gy) TBI. For patients who received low dose TBI, the incidence was comparable to myeloablative chemotherapy alone, but still 2-fold higher than general population.

Author Year	Ref	Year of HCT/ duration of FU	Study cohort	Age at HCT	No of MPT	Primary diagnosis of patients who developed MPT	Type of cancer	Interval between HCT to MPT	Donor for patients who developed MPT	Conditioning for patients who developed MPT	Outcome of patients with MPT	Remarks
Omori 2013 Single centre Tokyo, Japan	[46]	1995-2010 Median duration of FU: 10.5 years (max 16.4 years)	370 113 AML 117 ALL 39 lymphoma 34 MDS 41 CML 6 dyshematopoiesis All allogenic	Adult and paediatric cohorts Median: 36 years (range 1-72 years)	11 MPT in 10 patients	3 ALL 2 AML 3 lymphoma 2 MDS	1 thyroid papillary carcinoma 1 submaxillary gland tumour 2 oesophageal cancer 1 oral cavity carcinoma 2 gastric cancer 1 ureteral cancer 1 head and neck cancer 1 border malignant ovarian tumour 1 extragonadal germ cell tumour	Median: 6.8 years (range, 1.4 to 15.2 years)	Allogenic HCT Donor details: NA	All had TBI	3 died of MPT 1 died of aspiration pneumonia	Incidence of invasive solid MPT 2.15±1.22 and 6.46±2.82% at 5 and 10 years post-HCT

Author Year	Ref	Year of HCT/ duration of FU	Study cohort	Age at HCT	No of MPT	Primary diagnosis of patients who developed MPT	Type of cancer	Interval between HCT to MPT	Donor for patients who developed MPT	Conditioning for patients who developed MPT	Outcome of patients with MPT	Remarks
Rizzo 2009 CIBMTR and Seattle	[27]	1964-1996 Duration of FU: NA	28874 (excluded Fanconi anaemia and PID) 5916 (20.5%) ALL 7461 (25.8%) ANLL 7594 (26.3) CML 452 (1.6%) other leukaemia 1152 (4.0%) NHL 242 (0.8%) HL 507 (1.8%) Myeloma 158 (0.5%): other malignancies 2842 (9.8%)	Adult and paediatric cohorts Median: 27 years (range 0.08 -72.4 years)	Excluded PTLD, BCC and leukaemia/ MDS 189 MPT	NA	17 carcinoma *in situ* of skin 19 invasive SCC of skin 27 oral/pharyngeal 18 melanoma 18 braub 16 thyroid 13 breast 9 female genital 8 bronchus/ lung 7 liver 7 soft tissue 6 bone/joint 3 oesophagus 3 testes 2 colon 4 rectum /rectosingmoid/ anus 12 other solid cancers	NA	Allogenic HCT Donor details: NA	NA	NA	CI of solid MPT: Competing risk analysis: 1% at 10 years, 2.2% at 15 years, 3.3% at 20 years post-HCT Kaplan-Meier analysis: 2.5% at 10 years, 5.8% at 15 years, 8.8% at 20 years post-HCT Latency: 65 MPT occurred 1-4 years and 100 ≥ 5 years post-HCT The rate of solid MPT was at 2.1-fold higher than general population and reached 3-fold among patients followed for ≥ 15 years post-HCT

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			SAA 1298 (4.5%) MDS/MPD 906 (3.1%) Haemoglobinopathies 346 (1.2%) other All allogeneic HCT 631 (2.2%) Twin 22030 (76.3%) MSD 2939 (10.2%) MFD 3066 (10.6%) UD 208 (0.7%) other/uncertain									Risk factors: Conditioning radiotherapy (TBI or limited field): non-SCC tumour – RR 2.3 for TBI Age at HCT: RR 55.3 for < 10 years; RR 6.2 if 10-19 years; 4.8 if 20-29 years; no excess risk if > 30 years cGvHD: SCC – skin RR 11.0, oral RR 5.3 Male: SCC – skin RR 11.9, oral RR 2.8 Most cases of CNS, thyroid, bone, soft tissue MPT occurred in patients who underwent HCT at < 17 years of age

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Landgren 2009 CIBMTR and Seattle (update of Curtis, 1999)	[45]	1964-1996 Median duration of Fu NA	26901 (excluded PID, inherited cancer predisposition syndromes, initial diagnosis of NHL) 11582 ALL 14736 ANLL 14916 CML 5576 AA 6992 Other All allogeneic HCT 20873 (77.6%) MSD 2828 (10.5%) MMFD 3005 (11.2%) UD 195 (0.7) other/uncertain	Adult and paediatric cohorts Median: 26.6 years (0.1-68 years)	127 PTLD Other MPT not included	NA	PTLD	105 (83%) occurred within first year post-HCT 22 (17%) late onset, 1- >10 years post-HCT	NA	NA	NA	The observed to expected ratio was 29.7% <u>Risk factors:</u> T cell depletion: RR 3.1 – 9..4 Use of ATG: RR 3.8 HLA mismatch in presence of T-cell depletion/ATG use: RR 3.8 Acute (RR 1.7) and chronic (RR 2) GvHD Less effect when T-cell depletion used agents which also remove B cells.

Author Year	Ref	Year of HCT/ duration of FU	Study cohort	Age at HCT	No of MPT	Primary diagnosis of patients who developed MPT	Type of cancer	Interval between HCT to MPT	Donor for patients who developed MPT	Conditioning for patients who developed MPT	Outcome of patients with MPT	Remarks
Cohen 2007 EBMT	[44]	1985-2003 Median duration of FU: 12.7 years 25th centile: 10.3 years 75th centile 16.5 years	70859 57999 (82%) haematological cancer 8416 (12%) solid tumour 4391 (6%) AA 53 (0.1%) unknown 317771 (45%) allogenic 38988 (55%) autologous 100 (0.1%) unknown	Adult and paediatric cohorts 15% <10 10% 10-20 75% >20	32 thyroid carcinomas (23 papillary, 9 follicular)	10 ALL 7 CML 4 AML 1 MDS 1 NHL 1 unclassified leukaemia 3 AA 4 neuroblastoma 1 breast cancer Median age at HCT: 11.2 years (range, 1.7 to 51.3 years)	32 thyroid carcinomas Median age at diagnosis of MPT: 23.5 years (range, 8.8 to 52.2 years)	Median: 8.5 years (range, 0.6 to 22.2)	23 allogenic (21 MSD; 2 unrelated) 9 autologous 31 unmanipulated marrow 1 PBSC	7 chemotherapy alone 23 TBI + chemotherapy 1 thoracoabdominal irradiation + chemotherapy	25 total thyroidectomy 5 subtotal thyroidectomy 1 Partial 1 lobectomy 23 radioactive iodine ablation 29 alive and disease free after a median period of 5.5 years from MPT (range, 0.3 to 11.5) 2 died of	CI of thyroid MPT ~0.05% at 20 years post-HCT (0.2% in patients 0-10 years of age at HCT. 18 (56%) presented with palpable nodules 9 (28%) was asymptomatics and diagnosed only on ultrasound surveillance. Risk factors: Age at HCT: RR 24.6 for < 10 years vs > 20 years TBI or thoraco-abdominal radiotherapy (RR 3.4) Females RR 2.8 vs

Author Year	Ref	Year of HCT/ duration of FU	Study cohort	Age at HCT	No of MPT	Primary diagnosis of patients who developed MPT	Type of cancer	Interval between HCT to MPT	Donor for patients who developed MPT	Conditioning for patients who developed MPT	Outcome of patients with MPT	Remarks
											relapse of primary disease 1 died of progression of MPT	males cGvHD RR 2.9
Baker 2003 (update of Bhatia, 1996) Single centre study Minnesota	[49]	1974-2001 Median duration of follow-up: 5 years (range, 0.5 – 25 years)	3372 211 AA 117 PID 215 IEM 582 ALL 594 AML 602 CML 119 MDS 342 NHL 124 HD 102 neuroblastoma 138 Breast cancer 226 other	Adult and paediatric cohorts Median: 24 years (range, 0.1 to 67)	147 MPT in 137 patients	NA	44 PTLD 36 AML/MDS 5 other leukaemia/ lymphoma 62 solid MPT Type of solid MPT 4 adenocarcinoma 11 BCC 4 breast 1 carcinoid (rectal) 5 carcinoma in situ	PTLD Median: 0.3 years (range, 0.1 to 7.3 years) NA for MDS/ AML and solid MPT	NA	NA	PTLD: 79% (34/43) died AML/MDS 79.4% (27/34) died Solid MPT: 42% died of solid MPT	CI of MPT: 5.9% at 20 years post-HCT, increasing by about 2% in each successive 5 years follow-up period. Most solid MPT occurs after 5 years, 3.8% at 20 years Risk factors for PTLD: MMFD (RR 9.0) PID (RR 2.7) CML (RR 2.5)

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			1287 MFD 120 MMFD 373 MUD 399 MMUD 1193 autologous				2 carcinoma (primary unknown) 1 CML 1 CNS, astrocytoma 1 CNS, ependymoma 1 CNS, glioma 1 CNS, neuroectodermal tumour 4 HD 3 parotid MEC 1 neuroblastoma 1 papillary thyroid carcinoma 1 renal cell carcinoma 1 sarcoma, bone 1 angiosarcoma					in vitro TCE (RR 4.0) Grade 3-4 GvhD (RR 2.4) Risk factors for solid MPT: Age ≥ 20 years at HCT (RR 2.0) TBI not significant Risk factors for AML/MDS: 230 of 34 had autologous HCT Risk highest for PBSC (RR 3.1)

Author Year	Ref	Year of HCT/ duration of FU	Study cohort	Age at HCT	No of MPT	Primary diagnosis of patients who developed MPT	Type of cancer	Interval between HCT to MPT	Donor for patients who developed MPT	Conditioning for patients who developed MPT	Outcome of patients with MPT	Remarks
							1 fibrosarcoma 1 liposarcoma 1 rhabdomyosarcoma 1 lung SCC 1 oral cavity SCC 1 skin SC					
Bhatia 2001 Single centre City of Hope	[43]	1976-1998 Median duration of FU: 3.3 years (range, 0.1 to 21.1 years)	2129 327 ALL 648 AML 447 NHL 241 HD 392 CML 73 AA 1155 related donor 213 UD 759 autologous	Adult and paediatric cohorts Median: 33.9 years (range, 1.5-71.5 years)	29 solid MPT Excluded PTLD and haematological malignancies	2 ALL 5 AML 1 AA 1 NHL 5 CML	3 SCC 6 BCC 4 cervix uteri 2 salivary gland 3 SCC of oral cavity 2 breast cancer 2 liver cancer (had hepatitis C) 2 thyroid 1 astrocytoma 1 malignant fibrous histiocytoma	Median, years (range) Cervix, 3.3 (1.6-9.7) Thyroid, 12.7 (7.5-18) Oral cavity, 7.6 (4.7-11.7) Liver, 10.8 (6.7-14.9) Breast, 9.9 (2.6-17.1)	NA	NA	NA	CI of solid MPT: 1.6% at 5 years post HCT; 6.1% at 10 years post HCT Allogeneic: 6.4% at 10 years post-HCT Autologous: 1.6% at 10 years post-HCT All 6 skin SCC had cGVHD

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							1 SCC oesophagus 1 synovial sarcoma					
Socie 2000 CIBMTR and Seattle	[24]	1964-1992 Median duration of FU for patient survived > 1 year: 3.6 years (range, 1- 20.7 years	3182 2022 (63.5%) ALL 1130 (35.5%) ANLL 30 unspecified leukaemia 2385 MSD 96 syngeneic 53 MFD 492 MMFD 125 UD 20 other/ uncertain	Paediatric cohort < 17 years	45 (1.4%) 1 Melanoma in situ	11 ALL 9 ANLL Age at HCT Median: 5.8 years (range 0.4 to 16.1 years) 12 ALL 11 ANLL 2 unspecified leukaemia Age at HCT Median: 8.2 years (range,	20 PTLD 25 invasive solid cancers 9 brain cancer 5 thyroid papillary carcinoma 3 tongue SCC 3 melanoma 2 salivary MEC	Median: 1.5 years 15 - first year post-HCT 4 - between 12 and 18 months 1 - 4.9 years post-HCT Median: 6 years (range, 0.3 to 14.3 years)	Allogenic HCT Donor details: NA 20 MSD 3 twin donors 2 MMFD	NA All had radiation	All died 12 died (all patients with brain MPT died)	CI of invasive solid MPT 0.9%, 4.3% and 11% at 5, 10, 15 years post-HCT Solid MPT was associated with age at HCT <10 years of age (RR 3.7) and high dose TBI (RR 3.1) Chronic GvHD lowered risk of solid tumours (RR 0.2) PTLD was associated with moderate/severe cGvHD (RR 6.5),

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						0.3-14.3 years)	2 osteosarcoma 1 MFH					MUD and MMFD (RR 7.5), TCD ($$ 4.8), and ATG (RR 3.1)
Kolb 1999 EBMT	[42]	Before 1986 Median duration of FU: 10.7 years (range, 5- 22.1 years	1036 302 AML 212 ALL 208 CML 185 AA 35 lymphoma 9 IEM 32 solid tumours All allogeneic	Adult and paediatric cohorts Median: 21 years (range, 1 to 51.9 years)	53 (5.1%)	NA	14 skin 7 oral 5 gut 5 thyroid 6 uterine/ cervix 4 breast 3 brain 1 leukaemia	NA	52 allogenic 1 autologous	8 chemotherapy only 45 radiation plus chemotherapy	10 died	Cumulative incidence of MPT 3.5±0.6% at 10 years post-HCT and 12.8±2.6% at 15 years post-HCT. The rate of MPT was 3.8-fold higher that in an age-matched control population, More common in older patients and patients with cGvHD

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Curtis 1999 CIBMTR and Seattle	[41]	1964-1992 Duration of FU: NA	18014 (excluded NHL, Fanconi and PID) 4139 (23%) ALL 5065 (28%) ANLL 4770 (26.5%) CML 2114 (11.7%) AA 1926 (10.7%) Other 16815 (93.3%) MFD/ MMFD 1068 (5.9%) UD 131 other/ uncertain	Adult and paediatric cohorts Median: 25 years (range, <1 to 72 years)	78 PTLD	Early onset PTLD: 16 ALL 15 AML 19 CML 5 AA 5 MDS 2 IEM 1 HD I haemoglobinopathy Late onset PTLD: 5 ALL 4 AML 4 CML 1 AA	Not relevant	64 (82%) first year post HCT 14 – late onset 1 to 8.6 years post-HCT	NA	74 had TBI	Early onset PTLD: 55 (86%) died Late onset PTLD: 11 (79%) died	CI of PTLD: 1.0% at 10 years post-HCT Risk factors: Unrelated or MMFD: RR 4.1 TCD of donor marrow: 12.7 ATG: RR 6.4 Anti-CD3 monoclonal antibody: RR 43.2 Grade II-IV aGvHD: RR 1.9 Radiation based conditioning: RR 2.9 Multiplicative effect of risk factors: 2 major risk factors: RR 8.0 ≥ 3 factors: RR 22%

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Curtis 1997 CIBMTR and Seattle	[40]	1964-1992 Median duration of FU: 3.5 years (range, >1- 25 years)	**19229** (excluded NHL, Fanconi and PID) 4245 (22%) ALL 5208 (27.1%) ANLL 4885 (25.4%) CML 729 (3.8) NHL 561 (2.9%) other cancer 643 (3.3%) MDS 2159 (11.2%) AA 799 (4.2%) Other 533 (2.8%) syngeneic 15217 (79%)	Adult and paediatric cohorts Median: 25.5 years (range, 0.2 to 67 years)	80 solid MPT	16 ALL 28 ANLL 14 CML 8 AA 4 lymphoma/other	17 Buccal cavity/pharynx (1 neuroblastoma of nasal cavities; 4 MEC) 1 colon 2 rectum 3 liver (2 malignant fibrous histiocytomas) 2 lung 7 breast 1 cervix 1 uterine 2 testis 11 brain (4 astrocytoma, 6 glioblastoma, 1 PNEC) 8 thyroid 9 bone and connective tissue (3 chondrosarcoma,	NA	NA	NA	36 died	CI of solid MPT: 2.2% at 10 years post-HCT and 6.7% at 15 years post-HCT Ratio to observed to expected cases: 2.7 (p<0.001) Risk factors: Younger age at HCT Higher dose TBI Chronic GvHD Male

Author Year	Ref	Year of HCT/ duration of FU	Study cohort	Age at HCT	No of MPT	Primary diagnosis of patients who developed MPT	Type of cancer	Interval between HCT to MPT	Donor for patients who developed MPT	Conditioning for patients who developed MPT	Outcome of patients with MPT	Remarks
			MSD 2265 (11.8%) MMFD 1079 (5.6%) UD 135 (0.7%) other/uncertain				1 osteosarcoma, 2 rhabdomyosarcoma, 2 fibrosarcoma, 1 unspecified) 11 melanoma 5 other					
Bhatia 1996 Single centre Minnesota	[39]	1974-1995 Median duration of FU: 3.1 years (range, 0.6- 18.8 years)	**2150** 451 ALL 403 AML 419 CML 72 MDS 201 NHL 86 HD 75 NHL 75 NBL 30 Breast cancer 150 AA 92 PID 91 IEM 80 others	Adult and paediatric cohorts Median: 20 years (range, 0.2 to 67 years)	51 (2.4%) developed 53 MPT	26 leukaemia 25 lymphoma 8 PID 1 AA 1 IEM	22 EBV-related PTLD 11 AML/MDS 2 NHL 1 HD 17 solid MPT 3 melanoma 2 brain tumour 3 BCC 1 SCC 1 osteosarcoma 1 papillary carcinoma of thyroid 1 malignant	PTLD Median: 0.2 years (range, 0.1 0 3.0 years) AML/MDS Median: 3.0 (range 0.3 to 9 years) Solid tumours: Median: 4.0 (0.2 – 13 years)	38 related donor 6 UD 18 autologous	NA	36 died	CI of MPT: 9.9% at 13 years post-HCT CI of solid MPT: 5.6% at 13 years post-HCT PTLD plateaued at 1.6% at 4 years, AML/MDS at 2.1% 9 years Risk factors: Solid MPT: TBI (RR 6.0); cGVHD was not a risk factor for skin MPT AML/MDS: PBSC (RR 5.8), age >35

Author Year	Ref	Year of HCT/ duration of FU	Study cohort	Age at HCT	No of MPT	Primary diagnosis of patients who developed MPT	Type of cancer	Interval between HCT to MPT	Donor for patients who developed MPT	Conditioning for patients who developed MPT	Outcome of patients with MPT	Remarks
			1063 MFD/ MMFD 337 UD 750 autologous				fibrous histiocytoma 1 breast cancer 1 prostate cancer 1 carcinoma in situ of cervix and vulva 1 adenocarcinoma of unknown primary					at HCT (RR 3.5) PTLD: in vitro TCD (RR 11.9), ATG (RR 5.9), MMD (RR 8.9), **PID (RR 2.5)**

Author Year	Ref	Year of HCT/ duration of FU	Study cohort	Age at HCT	No of MPT	Primary diagnosis of patients who developed MPT	Type of cancer	Interval between HCT to MPT	Donor for patients who developed MPT	Conditioning for patients who developed MPT	Outcome of patients with MPT	Remarks
Witherspoon 1989 Single centre Seattle	[38]	1970-1987 Duration of FU: NA	**2145** 1926 leukaemia 320 AA 152 syngeneic 1980 MFD/ MMFD 13 UD 101 autologous	Adult and paediatric cohorts Age at HCT Median: 19 years (range, 2-58)	35 (1.6%)	15 ALL 10 ANLL 4 CML 4 AA 1 Hodgkin's 1 myelofibrosis	16 NHL 6 leukaemia 3 glioblastoma 3 melanoma 3 SCC 1 hepatic adenocarcinoma 1 adenocarcinoma of rectum 1 lung adenocarcinoma 1 invasive vulvar carcinoma	Median: 1.0 year (range, 1.5 months to 13.9 years)	NA	32 had TBI	30 died of secondary cancer 5 survived after successful treatment of secondary cancer (2 melanoma, 1 BCC, 1 vulvar carcinoma, 1 B-NHL)	Age-adjusted incidence of secondary cancer was 6.69 times higher than that of primary cancer in the general population Risk factors: acute GvHD, ATG, anti-CD3 monoclonal body, TBI, T cell depletion, HLA mismatch

AA: aplastic anaemia; ALL: acute lymphoblastic leukaemia; ANLL: acute nonlymphoblastic leukaemia; AML: acute myeloid leukaemia; BCC: basal cell carcinoma; Bu: Busulfan; CB: cord blood; CGD: chronic granulomatous disease; CI: cumulative incidence; CIBMTR: Centre for International Blood and Marrow Transplant Research; CML chronic myeloid leukaemia; CNS: central nervous system, Cy: cyclophosphamide; EBV: Epstein-Barr virus; Flu: Fludarabine; FU: follow-up GvHD: graft-versus-host disease; HCC: hepatocellular carcinoma; HD: Hodgkin's lymphoma; HLH: haemophagocytic lymphohistiocytosis; JAK3: Janus Kinase 3; IEM: inborn error of metabolism; JMML: juvenile myelomonocytic leukaemia; LAD1: leucocyte adhesion deficiency type 1; MDS: myelodysplastic syndrome; MEC: mucoepidermoid carcinoma; Melp: Melphalan; MFD: mismatched family donor; MFH: mismatched family donor; MSD: matched sibling donor; MMD: mismatched donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; MPT: malignancy post-transplant; NA: not available; NBL: neuroblastoma; NHL: non-Hodgkin's lymphoma; NFKB2: nuclear factor kappa B 2; PBSC: peripheral blood stem cell; PID: primary immunodeficiency; PNEC: primitive neuroectodermal cancer; PTLD: post-transplant lymphoproliferative disease; RCC: renal cell carcinoma; RMS; rhabdomyosarcoma; RR: relative risk; SCID: severe combined immunodeficiency; SCC: squamous cell carcinoma; TBI: total body irradiation; TCD: T cell depletion; Thio: thiotepa; Treo: treosulfan; UD: unrelated donor; WAS: Wiskott-Aldrich syndrome

Table 3 Reported malignancy post haematopoietic stem cell transplant in patients with primary immunodeficiency

Author Year	Year of HCT/ Duration of FU	Ref	Study cohort	Age at HCT	No of post-HCT cancer	Primary diagnosis	Type of cancer	Interval between HCT to malignancy	Donor	Conditioning	Outcome	Remarks
Unni 2018	NA	[48]	944	NA Children	12 (1.27%) non-PTLD malignancy Age at HCT: 85 months (range, 4-204 months)	4 SCID (RAG2, JAK3, 2 unknown) 1 CGD 1 CD40 ligand 1 Griscelli/ HLH systemic 1 GATA2 1 LAD1 1 MHC class I 1 NEFB2 systemic 1 WAS	1 ALL, 1 AML, 1 right occipital Ewing sarcoma, 1 embryonal RMS of right cheek BCC (ear) and left lower leg SCC in situ RCC JMML Toe melanoma RCC Parotid MEC Parotid MEC SCC (gastrostomy site)	Median: 3.75 years (range, 3 months to 11.2 years)	4 MSD marrow 4 MUD marrow 1 MMUD marrow 2 MUD PBSC 1 matched CB	7 Flu-Melp 3 Flu-Treo 1 Bu-Flu 1 Bu-Cy 10 alemtuzumab 2 no serotherapy None had TBI	2 died 10 alive with median follow-up of 13.2 years (range 2 years 1 month to 18 years)	RAG2 SCID with ALL had 100% recipient myeloid chimerism; leukaemia was recipient in origin. Griscelli with JMML had 100% recipient myeloid chimerism; leukaemia was recipient in origin.

Author Year	Year of HCT/ Duration of FU	Ref	Study cohort	Age at HCT	No of post-HCT cancer	Primary diagnosis	Type of cancer	Interval between HCT to malignancy	Donor	Conditioning	Outcome	Remarks
Nelson 2017	1982-2007 Median duration of FU: 4.5 years (range, 0 to 25.4 years)	[47]	318 71 acquired AA 51 inherited AA 69 SCID 24 WAS 37 other PID 14 HLH 14 thalassaemia 38 IEM 149 MFD 52 MMFD 78 MUD 38 MMUD 1 unknown	Median: 3 years (range, 0-14 years)	6 (1.9%)	1 AA 2 FA 1 CGD 1 SCID 1 Thalassaemia	2 leukaemia 4 solid tumours	Median: 9.2 years (range, 0.4-14.5 years)	4 MFD 2 MMFD	2 had radiation	3 died	Cumulative incidence of MPT was 0.3±0.3% at 5 years post-HCT and 2.3±1.2% at 10 years post-HCT
Kamani 2011 CIBMTR	1968-2003 Duration of FU: NA	[51]	2266 1075 SCID 360 WAS 831 Others	Median: 1 year (range, 1.2 months to 47 years)	52 (2.3%) all malignancy Median age at)	25 (2.35%) SCID 12 (3.3%) WAS 15 (1.8%) other	45 PTLD (17 confirmed positive EBV) 3 MDS 1 AML	Median: 3.7 months (range, 0.9 to 169.6 months)	9 family donors 11 MUD 19 haploidentifical donors 10 MUD/ MFD	22 BuCy 1 BuCyEtoposide 8 TBICy 5 Cy 9 none 1 CyCytarabine 1 Flu	40 (77%) died Cause of death: 29 post-transplant malignancy	PID patients were at a relatively low risk of developing

Author Year	Year of HCT/ Duration of FU	Ref	Study cohort	Age at HCT	No of post-HCT cancer	Primary diagnosis	Type of cancer	Interval between HCT to malignancy	Donor	Conditioning	Outcome	Remarks
			630 MSD 961 other family donors 528 UD		HCT: 15.6 months (range 1.2 months to 265.2 months		1 SCC 1 HCC 1 brain tumour		3 fetal 40 marrow 5 CB 2 PBSC 3 fetal 2 unknown 29 had ex-vivo T depletion	1 FluCy 1 FluMelpThio 1 Methyl+Campath 2 unknown	4infection 3 GvHD 4 unknown	malignancy post-HCT compared to their historical risk of cancer. T cell depletion appeared to correlate with PTLD development.

ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia; BCC: basal cell carcinoma; Bu: Busulfan; CB: cord blood; CGD: chronic granulomatous disease; Cy: cyclophosphamide; EBV: Epstein-Barr virus; Flu: Fludarabine; GvHD: graft-versus-host disease; HCC: hepatocellular carcinoma; HLH: haemophagocytic lymphohistiocytosis; IEM: inborn error of metabolism; JAK3: Janus Kinase 3; JMML: juvenile myelomonocytic leukaemia; LAD1: leucocyte adhesion deficiency type 1; MDS: myelodysplastic syndrome; MEC: mucoepidermoid carcinoma; Melp: Melphalan; Methyl: methylprednisolone; MFD: mismatched family donor; MSD: matched sibling donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; NA: not available; NFKB2: nuclear factor kappa B 2; PBSC: peripheral blood stem cell; PID: primary immunodeficiency; PTLD: post-transplant lymphoproliferative disease; RCC: renal cell carcinoma; SCID: severe combined immunodeficiency; SCC: squamous cell carcinoma; TBI: total body irradiation; Thio: thiotepa; Treo: treosulfan; WAS: Wiskott-Aldrich syndrome

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