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

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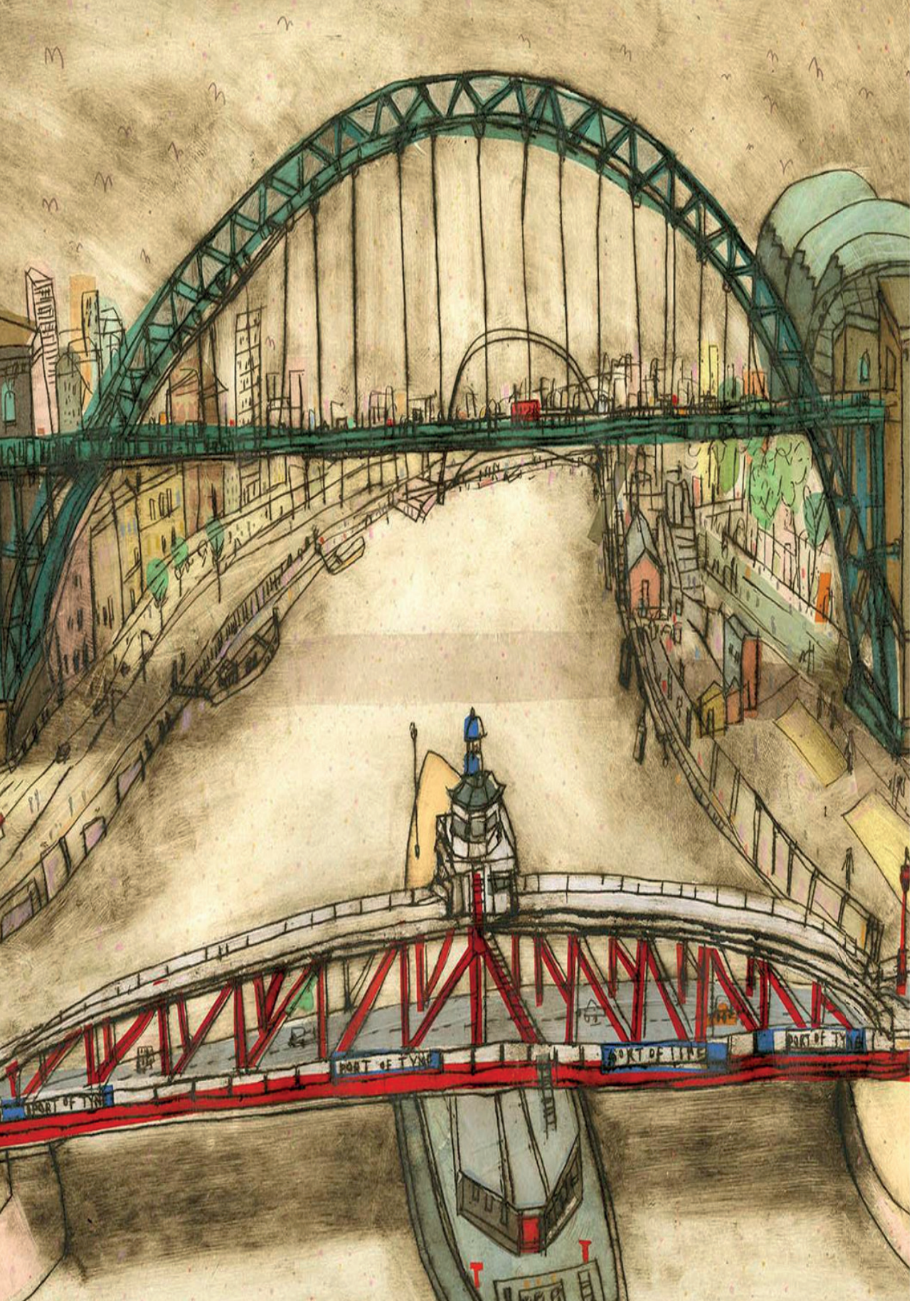
Part 5

Summary and future perspectives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Chapter 10

Summary

This year, 2020, marks 52 years since the first allogeneic haematopoietic cell transplantations (HCTs) were performed for primary immunodeficiencies (PID) in 1968. HCT is now an established curative treatment for many inborn errors of immunity (IEI).

Chapter 1 describes the principles of HCT in IEI, transplant strategies in IEI (including donor selection, stem cell source, graft engineering, and conditioning), early transplant complications and late effects.

Chapter 2 reports transplant survival, long-term graft function, immune reconstitution and autoimmune disease post-transplant in 55 children with CGD who were transplanted in Newcastle upon Tyne. The study highlighted excellent survival after allogeneic HCT for children with CGD and younger age (<5 years at HCT) was associated with 100% survival. Alternative donors using unrelated and parental haploidentical donors were associated with excellent survival comparable to family donors. There were no late deaths. Of the 11 survivors who were older than 21 years of age, 6 (55%) had unassisted successful pregnancy themselves or with their partners (4 received Busulfan-Cyclophosphamide, 1 Busulfan-Fludarabine and 1 had Fludarabine-Melphalan). Our cohort confirmed that HCT performed in an experienced immunology transplant center is safe and provides long-term cure for children with CGD. These findings have been confirmed by a recent EBMT multicentre study which showed younger patients and well-matched donors were associated with improved survival chance in 721 patients with CGD. (1) In Newcastle, all newly diagnosed CGD patients are recommended for HCT with either a matched donor or a haploidentical donor if no suitable matched donor is available.

Chapter 3 analyses the clinical presentations, laboratory features, transplant survival and long-term disease outcomes of 25 patients with MHC class II deficiency who underwent first HCT in Newcastle upon Tyne between 1995 and 2018. Whilst children with MHC class II deficiency usually have severe CD4+ T-lymphocytopenia, this study showed 6 (24%) had a normal CD4+ T-lymphocyte and 8 (32%) had a normal CD4:CD8 ratio. Autoimmunity was the first presentation of 2 patients and these 2 patients developed macrophage activation syndrome prior to transplant, which has not been reported previously. Overall survival (OS) has improved to 94% for children who were transplanted after 2008 (n=19), compared to 33% prior to 2008. For HCT after 2008, the transplant survival was comparable between matched donor and haploidentical donor transplant recipients. Although latest $CD4^+$ T-lymphocyte number was significantly lower in transplant survivors (n=14) compared to post-transplant disease controls, all survivors were off immunoglobulin replacement, had protective vaccine responses and did not have any significant infection or autoimmunity. This study showed that transplant survival for MHC class II deficiency has improved significantly in the modern era of HCT. Long-term health outcome after HCT for MHC class II expression deficiency is

good. HCT should be performed as early as possible after the diagnosis, before the onset of disease-related organ damage.

Chapter 4 describes the emerging indications and reported transplant outcomes in monogenic autoimmune diseases. While indications for HCT for SCID and specific PIDs such as CGD are well-defined, the indications for HCT in monogenic autoimmune diseases are less straight forward. This chapter summarized a literature-based update on indications and outcomes of HCT for monogenic autoimmune diseases. As the number of monogenic autoimmune disease is rapidly expanding with the availability of next generation sequencing, international collaborations are important to develop a standardized treatment guideline for such rare diseases.

Chapter 5 reports the first and largest series comparing transplant outcomes according to ex-vivo T-cell depletion methods in children with IEI over the last 30 years. Historically poor survival following mismatched grafts for non SCID IEI using the old techniques is well known. This report clearly demonstrates the improvement in transplant survival with more recent techniques and the successful use of CD3+ TCR αβ/CD19 depletion in patients with a diverse range of non-SCID IEI. Importantly for many conditions we have also demonstrated better myeloid chimerism. TCR αβ/CD19 depletion was associated with low rates of aGVHD and no cGVHD even in patients not given any post-transplant GVHD prophylaxis, which for example, removes the renal toxicity associated with calcineurin inhibitors. However further improvements are necessary to decrease morbidity and mortality associated with viral infections.

Chapter 6 compares the transplant outcomes according to T-replete HLA-matched grafts using alemtuzumab (n=117) and in vitro T-depleted HLA-mismatched grafts using TCR αβ/CD19 depletion (n=47) in children with IEI who underwent first HCT between 2014 and 2019. In children who were younger than 5 years of age at HCT, the 3-year overall survival was comparable between T-replete grafts (88%, 76-94%) and T-depleted grafts (87%, 64-96%). In contrast, for children who were older than 5 years of age at HCT, the OS was significantly lower in T-depleted grafts (55%, 23-78%), compared to T-replete grafts (87%, 68-95%) (p=0.03). Grade III-IV aGvHD was observed in 8% of T-replete marrow, 7% of T-replete PBSC, 14% of T-replete CB and only 2% of T-depleted PBSC (p=0.73). Higher incidence of viraemia (p<0.001) and delayed CD3 reconstitution (p=0.003) were observed after T-depleted graft HCTs. Similar to data in children with leukaemia (2), these data indicate that mismatched or haploidentical donor transplant after TCR αβ and CD19 depletion represents a reasonable alternative for children with IEI in need of an allograft.

Chapter 7 presents the largest analysis to document post-HCT autoimmune cytopenia (AIC) from a cohort of 502 children with IEI over the past three decades. The 5-year cumulative

incidence of post-HCT AIC in our cohort was 9%, which is higher than the majority of reported results in paediatric cohorts. (3-6). Mismatched donor, alemtuzumab, ATG and graft-versus-host disease were associated with post-transplant autoimmune cytopenia. Use of a reduced toxicity conditioning regimen and *ex vivo* T-cell depletion were not associated with post-HCT AIC. The majority of patients achieved complete remission with first line therapy. Impaired B-lymphocyte function after rituximab was observed in 5 (42%) and these patients remained on immunoglobulin replacement after a median of 10.5 years (ranged 2.6 to 15.2 years) following the last dose of rituximab.

Chapter 8 reports the incidence, risk factors and outcomes of non-haematological autoimmunity in a cohort of 596 children with IEI from three institutions with significant experience of transplanting these diseases. The cumulative incidence (CIN) of post-HCT AD was 11% at 8 years post-HCT. The median onset of post-HCT non-haematological autoimmune disease was 2.2 years (0.12 to 9.6 years). Type of autoimmune diseases were: autoimmune thyroid disorders (62%), neuromuscular disorders (22%) and rheumatological manifestations (16%). All patients but one required treatment for post-HCT AD. After multivariate analysis, age at transplant (p=0.01) and an unmanipulated graft (p<0.001) were significant predictors for post-HCT AD. None of the T-depleted graft recipients developed post-HCT AD. Patients with a lower CD3+ count at 6 months post-HCT had a significantly higher incidence of post-HCT AD compared to disease controls. Overall, the manifestations of new AD after HCT are diverse and therefore, the diagnosis of post-HCT AD can be difficult and challenging as there is a broad range of differential diagnoses, including disease recurrence, chronic GvHD, infection and drug/conditioning-related side effects.

Chapter 9 reviews recently published literature focusing on the pattern of malignancy in children with IEI, incidence and risk factors for developing malignancy post-HCT for IEI and possible strategies to reduce the risks. Secondary malignancy post HCT for malignant disorders is well recognised and long-term follow including screening for malignancy is well established. Patients with IEI are at risk of developing malignancy as part of their underlying disorder. The most common form of malignancy is lymphoma. Survival from HCT for IEI has improved dramatically in recent years. The risk of developing malignancy after successful HCT is less clear. The risk of developing malignancy post HCT is dependent on patient-, disease- and transplant-specific factors. Some disorders are associated with specific malignancies for which the risk is not altered by changing the haematopoietic cell lineages. Age at HCT, chemotherapy agents and other drugs used, radiation, occurrence graft-versus-host disease, infections and degree of donor chimerism may all have a role in carcinogenesis. PID transplant survivors represent a unique cohort compared to transplant survivors of malignant and non-malignant haematological disorders.