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HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN GENETIC APLASTIC SYNDROMES

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The inherited (constitutional/genetic) bone marrow (BM) failure/aplastic anaemia (AA) syndromes are characterized by BM failure usually in association with one or more somatic abnormality.

This is a very heterogeneous group of disorders and their precise incidence/prevalence is unknown. The two syndromes in this group which are often associated with global BM failure are Fanconi anaemia (FA) and dyskeratosis congenita (DC).

Despite significant advances in our understanding of the pathophysiology of FA, allogeneic haematopoietic stem cell transplantation (HSCT) remains the only curative option for severe BM failure in FA patients.

There is now over 30 year HSCT experience in this disease. Initially, the use of conventional doses of cyclophosphamide was found to be associated with high transplant related mortality (TRM). This led to modification of HSCT protocols (reduced doses of cyclophosphamide and radiation – "Gluckman protocol") resulting in improved outcome.

FA patients are at high risk of developing cancers compared to patients with idiopathic aplastic anaemia.

This can now be explained in terms of the increased genomic instability observed in FA cells due to mutations in one of 12 FA genes (*FANCA* to *FANCM*) which have a key role in the "FA/BRCA pathway".

In order to further reduce TRM and minimise the risk of malignancy post-HSCT there has been an increase in the use low intensity-Fludarabine based protocols for FA patients. These protocols (including that at the Hammersmith Hospital) do appear to be associated with lower peri-tranplant toxicity and prompt engraftment but it remains to be seen whether they will be also associated with a lower risk of malignancy in the long-term.

Like FA, DC is also a very heterogeneous BM failure syndrome. X-linked recessive, autosomal recessive and autosomal dominant forms of DC are recognised. BM failure occurs at a high frequency and is also the main cause of premature mortality. Again there is some experience in the use HSCT in this disease.

Use of conventional HSCT protocols (which included radiotherapy) has been associated with unusual complications (including pulmonary and vascular pathology) and it now appears that this is partly related to defective telomere maintenance as two of the genes (*DKC1* and *TERC*) mutated in DC are key components of the telomerase complex and patients with DC have very short telomeres.

Recently there have been some encouraging reports of HSCT using low intensity-Fludarabine based protocols.

It remains to be seen whether they will be associated with significant long-term benefit in DC patients.