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Donor Derived Malignancies after Allogeneic Haematopoietic Stem Cell Transplantation: A Rare but Well Recognized Complication

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Introduction

Allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT) remains the only curative option for many malignant and non-malignant diseases. However, despite the advances in disease monitoring, conditioning regimens and supportive care, allo-HSCT is still associated with significant morbidity and mortality, with relapse constituting a major cause of post-transplant mortality, occurring in about 30% of patients.

In the majority of cases, relapse arises from the original malignant cells, which have evaded the toxicity of the conditioning and/or the graft-versus-leukaemia effect, whereas less frequently, relapsed disease carries different phenotypic or cytogenetic characteristics from the original disease, owing either to lineage switch or clonal evolution [1-5].

Description

Donor-Derived Malignancies (DDMs) is a rare entity, occurring in about 2%-5% of relapses, although its exact incidence remains unknown, due to the sporadic nature of the disease and the difficulties in disease confirmation. The vast majority of DDMs are of haematopoietic origin, with Acute Myeloid Leukaemia (AML) being the most common disorder. It is characterised by the emergence of a clonal population of haematopoietic cells of donor origin, which has either acquired genetic mutations conferring leukaemia (such as the DNMT3A, ASXL1, JAK2 and IDH2) or arose from a deleterious germline variant (such as the CEBPA, DDX41, GATA2 and RUNX1).

Donor age has also been suggested to play a critical role in DDM, with Clonal Haematopoiesis of Indeterminate Potential (CHIP), being more prevalent in aged donor cells. The increased proliferative demand of donor cells in the recipient has been hypothesised to be related to telomere shorting, which in combination with the underlying CHIP may lead to a leukaemic process (although there is no clear association between CHIP and DDM. However, not all studies have shown a positive correlation between donor age and risk of DDM. Similarly, the latency period before the development of DDM was found to be comparable between older and younger (age <55 years) donors in a large retrospective study. All the above have raised a significant ethical question of whether donors with CHIP should be excluded from donation. So far there is no consensus about donor NGS screening, but an open question remains [6-10].

Other factors contributing to the malignant transformation of healthy donor cells, include. Patient-related factors, such as the underlying disorder, creating a permissive environment for disease development, the cytotoxic and 'pre-malignant' effects of chemotherapy and/or radiation, the defective marrow stromal, allowing abnormal interactions between host cells (eg macrophages, fibroblasts) and donor stem cells and transplant-related factors, such as the conditioning and immunosuppressive regimens, the development of Graft-versus-Host Disease (GvHD), the suppressed T-cell responses, leading to impaired immune surveillance etc. Overall, DDM is considered to be a multifactorial process, with several putative mechanisms contributing to disease development. Genetic factors (such as germline predisposition) of donor cells may prime donated stem cells with a malignant tendency (first hit), with several patient-and transplant-related factors creating an aberrant environment (second/subsequent hits), contributing to the malignant evolution of donor stem cells.

Donor-derived solid tumours are exceedingly rare with only a few cases having been described, so far. Socie et al. reported four cases of oral squamous cell carcinoma that arose from donor-derived bone marrow cells, although they were unable to define which cell type gave rise to the cancer. Fusion of marrow cells with epithelial cells was excluded as no patient-related genetic material was identified, so it was hypothesised that the tumours derived from mesenchymal stem cells that were coinfused with haematopoietic stem cells within the marrow graft. A few other cases of donor-derived solid organ malignancies reported in the literature, refer to the development of advanced bile-duct cancer and oral squamous cell carcinoma, confirmed

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by immunostaining and Fluorescent *In situ* Hybridization (FISH) analysis for X and Y chromosomes. A more interesting care was reported by P. Tsirigotis et al., who presented a case of a patient after allo-HSCT who developed Small Cell Lung Carcinoma (SCLC) almost concomitantly with her donor. The authors concluded that the most likely explanation for this was the passive transmission of malignant cells from donor to recipient, through contaminated graft. In these lines, Brugger et al. Demonstrated that bone marrow-metastasised malignant SCLC cells can be mobilised with growth factors, such as the granulocyte colony-stimulating factor into peripheral blood, contaminating the haematopoietic stem cell grafts.

Conclusion

Focusing on elucidation of contributing factors to the development of DDM, involving both recipient (e.g. underlying haematological disorders or immune deficiency) and donor-related factors (e.g. presence of pre-malignant clones, advanced donor age and genetic abnormalities) is of paramount importance to improve long-term outcomes after allogeneic stem cell transplantation. Transplant-related factors (such as conditioning therapy, immunosuppressive regimens for GvHD prophylaxis etc) should also be investigated in an effort to better understand the interplay between donor, recipient and transplant and prevent catastrophic events, such as DDM.

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