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POSTER ABSTRACTS

711.CELL COLLECTION AND PROCESSING

The Non-Hematopoietic Content in Paediatric Autologous Hematopoietic Stem Cell Grafts Is Skewed Towards Regulatory Myeloid and Exhausted Phenotypes

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Autologous hematopoietic stem cell transplant (aHSCT) is a central component of paediatric brain tumours and high-risk neuroblastoma management. Standardly, chemotherapy and G-CSF are used to mobilize the CD34+ hematopoietic stem/progenitor cells (HSC), which are used to support hematopoietic recovery following dose chemotherapy. Clinically, the graft infused is defined by solely by the CD34+ content. The non-hematopoietic passenger cells makeup most of the graft and are a mixture of myeloid and lymphoid cells that are potentially biologically active in the post-transplant setting. Here we study the content of the graft, focusing on the phenotypes of the cell populations, to begin to look at how the non-hematopoietic cells may facilitate anti-tumor activity, affect the tumour microenvironment, and/or immune recovery post-transplant.

High parameter mass cytometry, with a custom 40-marker panel, was used to characterize 43 autologous cryopreserved grafts from children (median age 39 months, range 14-255 months) undergoing apheresis following chemotherapy and G-CSF mobilization. Healthy G-CSF-mobilized allogeneic donors (allograft) were used as a comparator group (n=10). Young children frequently have robust mobilization (peripheral blood CD34 count range from 100-1800 CD34/μL on day of collection) and generally one day collection will support multiple cycles of high dose therapy (target collections 20 x10 ^{6} CD34+ cells/kg and often over collecting in 2-3 blood volume processed). This results in a product that is rich in CD34+ cells, with intergraft heterogeneity (median 7%; range 0.7-31%), compared to the CD34+ content of allografts (median 1.1%; range 0.3-2.4%) (autograft vs allograft median CD34 difference $p<0.00005$; Wilcoxon unpaired). There was variability in the non-hematopoietic component in the autografts (median T cells 10.8%; range 0.6 - 51.7%, and median monocytes 18.8%; range 4.1 - 51.4%). The allogeneic products were found to have less variability (T cells: 19.9 - 56%; monocytes: 7.3 - 19.6%). Autografts had increased expression of T cell exhaustion markers, with a median 30.8% (range 14.7 - 88.1%) of T cells expressing TIGIT and 35.1% (range 13.1 - 75.9%) expressing PD1 compared to the allografts (median TIGIT: 15.7%; range 9.3 - 28.7% and median PD1: 11%; range 4.2 - 19.7%).

When grafts from high mobilizers (N= 21; >7% CD34+ cells) were analyzed by the actual number of cells infused they had had fewer regulatory cells: monocytic-myeloid derived-suppressor cells (M-MDSCs) (3.6x10 ^{7} cells/kg; range 0.5 - 73.8x10 ^{7}; $p<0.0003$), non-classical monocytes (0.9x10 ^{7} cells/kg; range 0.5 - 21.3x10 ^{7} cells/kg; $p< 0.002$) compared to the grafts from lower mobilizers (N = 22; <7.1% CD34+ cells) M-MDSC: median 7.7x10 ^{7}/kg; range 0.6 - 21.3x10 ^{7} cells/kg, non-classical monocytes: 1.7x10 ^{7} cells/kg; range 0.05 - 3.7x10 ^{7} cells/kg). T cells and NK cells did not differ between high and low mobilizers.

We are seeing significant differences in the regulatory cell populations infused in paediatric aHSCT based on the how robustly a patient mobilizes CD34+ cells after chemotherapy and G-CSF. It is not known whether these differences are clinically significant or affect anti-tumour immunity, tumour microenvironment perturbation, or immune recovery. With this high parameter mass cytometry strategy, we will be able to correlate engraftment kinetics and transplant outcomes (survival, relapse), which will allow us to re-envision how grafts should be optimally manufactured. Controllable variables include the timing of collection (earlier or later in the clinical course), alternative growth factor usage, enrichment or depletion of cell populations in the graft, or post-transplant growth factor administration. We suggest that the aHSCT graft can be thought of as an immunotherapy tool and not just for hematopoietic recovery.

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