Immune reconstitution and thymic function after allogeneic HSCT in Humans: critical issues and development

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Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) is widely used in the treatment of hematological malignancies. One of the main concerns is the profound and long-lasting immunodeficiency consecutive to this procedure. A potent immune reconstitution (IR) is essential to limit the infection risk and disease relapse. T-cell recovery through the thymic-dependent pathway, that involves generation of new naive T cell from donor-derived precursor cells, accounts for the durable reconstitution of the T-cell compartment (1). We and others have shown that long term T-cell reconstitution after HSCT is dependent on thymic function and is a slow process that can be influenced by several factors including: age of patients, HLA mismatches, unrelated donors, source of stem cell or occurrence of Graft versus Host Disease (GvHD) (1-4). Especially also, the setting of the graft is critical, as T-cell depleted and haploidentical HSCT (which is made possible through heavy T-cell depletion), will depend solely on neothymopoiesis for IR.

It is possible now to quantify thymic function \textit{ex vivo} in Humans by measuring thymic excision circles or “sjTREC”. These small circular DNA fragments are produced during recombination in the thymus of the genomic segments that encode the alpha chain of the T cell receptor (TCR). This episomal DNA is not replicated during cell division and so, the number of sjTREC in the peripheral blood is proportional to the number of lymphocyte leaving the thymus (or recent T-cell emigrants, “RTE”). The same principle applies to βTREC produced at early stages of T-cell differentiation during the TCR β-chain recombination (5). The ratio of sjTREC/βTREC indicates the proliferative ability of thymic progenitors within the thymus.

We recently precised some mechanisms of thymic impairement during acute GvHD (aGvHD) after allo-HSCT in Humans (3). Several keypoints emerged from that study raising the issue of thymic regeneration in that setting.

\textit{Acute GvHD delays the thymic dependent T lymphocyte recovery}
Although total T-cell number recovery was not significantly affected by the occurrence of aGvHD, the reconstitution of the CD4+CD45RA+ CD62L+ naïve compartment and the level of RTE
assessed by sjTREC were significantly lower in patients with aGvHD at 6 and 12 months after graft. T-cell repertoire data confirmed this result showing a deeper oligoclonality in case of aGvHD.

The thymus is very sensitive to acute GvHD
Although grade I aGvHD has low clinical manifestations and does not require corticosteroids, we observed that thymic output early after graft was significantly affected even in grade I as well as in grade II-IV compared to patients who did not experience aGvHD. This allowed to separate the impact of aGvHD from steroids treatment and also showed that clinical and pathological definition of aGvHD could be in some way different from its actual impact on primary lymphoid organs.

Acute GvHD effect on thymic function is reversible in younger patients
Age-related thymic involution begins with sex steroid increase at puberty. Age together with aGvHD could synergize to delay IR after allo-HSCT in adults. Actually, patients older than 25 years had the lowest sjTREC levels before transplantation and showed also a minimal recovery in presence or absence of aGvHD up to 1 year after graft. Recovery of sjTREC level was much more efficient in younger patients. aGvHD significantly impacted thymic output at month 6 after HSCT but thereafter thymic function recovered, reaching pretransplant values at one year after graft. Therefore we concluded that in younger patients (< 25 years of age), the thymic impact of an episode of aGvHD could be fully reversible. Conversely, chronic GvHD had a persistent effect on thymic function independently of the recipient’s age.

Acute GvHD induced delay in thymic function recovery is not primarily due to a default in intrathymic proliferation.
To study the mechanisms of aGvHD in thymic function recovery after allo-HSCT, we analyzed more in depth a series of 20 age-matched patients through the quantification of sj and βTREC, their ratio reflecting the αβ T-cells proliferation rate between β and α chain recombination7. We showed that βTREC levels declined in proportion to sjTREC, suggesting that the decreased thymic output during aGVHD is not due to a decline in thymocyte proliferation but is rather due to a blockade at an early thymocyte differentiation step before the TCR β-chain recombination.

Towards thymic rejuvenation in allo-HSCT
Our data showing that thymic function is impaired by aGvHD during the first months after transplantation may have consequences in terms of treatment. Decreasing incidence of aGvHD with aggressive GvHD prophylaxis and treatment, especially in young patients, could temper its effect
on IR. Alternatively, experimental models, especially in mice, but also now in human clinical trials, have shown that it is possible to increase thymic function after HSCT through the stimulation of the Growth Hormone (GH) pathway or Sex Steroid blockade, that are supposed to counterbalanced the effect of aging on the thymic function. Finally, treatments with exogenous IL7, FLT3L or Keratinocyte Growth Factor (KGF) have been shown to increase thymic output and promote T-cell precursor survival and naïve T-cell homeostasis (8, 9). The clinical use of these therapeutic agents, alone or in combination, could so be a way to alleviate, in allo-HSCT, the effect of age and GvHD on the restoration of a potent thymic function.

References