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REVIEW

Thymopoiesis following allogeneic stem cell transplantation: new possibilities for improvement

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Summary Treatment related mortality (TRM) has restricted the application of allogeneic hematopoietic stem cell transplantation (allo-SCT) as a treatment modality for patients with a variety of malignant and non-malignant hematological disorders. TRM is mainly caused by severe opportunistic infections, due to an impaired immune reconstitution. The extreme slow recovery of newly developed, donor stem cell derived naive T-cells is currently considered to be the most important determinant of the impaired immune competence after allo-SCT. Therefore, enhancing naïve T-cell recovery following allo-SCT by improving thymopoiesis has recently gained new interest. Possible strategies to improve thymopoiesis may include approaches to protect the nursing stromal compartment and approaches to directly stimulate the differentiation and proliferation of T-cell progenitors intra-thymically. Among the latter is interleukin-7 (IL-7), which has appeared promising in preclinical experimental settings and is expected to enter early clinical studies soon. Keratinocyte growth factor (KGF) is an epithelial growth factor that may protect the thymic epithelium and thereby may preserve it's support of thymopoiesis. KGF has been evaluated clinically in the setting of autologous stem cell transplantation and studies in the setting of allo-SCT are awaited in the near future.

Introduction

Allogeneic stem cell transplantation (allo-SCT) has been established as a powerful treatment modality for patients with hematological malignancies, aplastic anemia, and inborn errors of hematopoietic progenitor cells. Treatment related mortality (TRM), however, has restricted the application of allo-SCT. TRM is mainly caused by severe opportunistic infections, due to impaired immune reconstitution following allo-SCT. While epithelial barriers and granulocytes are restored within weeks following transplantation, B- and T lymphocytes may be deficient for a prolonged period of time. The extreme slow recovery of newly developed, donor stem cell derived, naive T-cells is currently considered to be the most important determinant of this impaired immune competence in the later time period after allo-SCT.[1–4] Especially older patients,

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those receiving an unrelated or mismatched related donor graft, and patients receiving a T-cell depleted graft may show a $CD4^+$ lymphopenia for more than 12 months after allo-SCT.

The slow recovery of naïve $CD4^+$ T-cells in older patients may be related to the natural involution of the thymus. Thymic output may be further compromised directly by radiotherapy and graft versus host disease (GVHD). Until recently, thymic output of T-cells could only be quantified by the measurement of $CD4^+CD45RA^+$ naïve T-cells in the peripheral blood. Enumerating naïve $CD4^+$ T-cells by flow cytometry may serve as a surrogate marker, but naïve $CD4^+$ T-cells may persist in the circulation for a prolonged period of time before converting to a memory phenotype.[5] Recently, however, episomal DNA circles generated during rearrangement of the gene segments encoding the T-cell receptor (TCR) have been proposed as markers for thymic output. These circles named TCR rearrangement excision circles (TRECs) are unique to T-cells, TRECs are stable, and not duplicated during mitosis and diluted out with each cellular division.[6–8] Thymic output as assessed by TRECs appeared critically affected by a history or presence of GVHD and by age.[9–10] Indeed, the most apparent abnormalities of T- and B-cell recovery were seen in patients with chronic GVHD.[11]

Thymopoiesis after allogeneic SCT

T-cell recovery in complete chimera's occurs either through a thymic-dependent, de-novo generation of naïve T-cells (thymopoiesis) or through a thymic-independent proliferation of mature T-cells (peripheral expansion) infused with the allogeneic stem cell graft.[1,12,13] De novo generation of T-cells is especially important for providing a new pool of naïve T-cells with a diverse T-cell receptor (TCR) repertoire.[1,14–20] Proliferation of mature T-cells infused with the graft is important for T-cell recovery in the early post-transplant period, but may also be associated with an oligoclonal TCR repertoire and aggrevation of GVHD.[21] In order to obtain adequate $CD4^+$ T-cell recovery and a broad TCR-repertoire after allogeneic SCT, restoration of thymopoiesis is essential. Aging, GVHD and radiotherapy may all compromise thymopoieisis after allogeneic SCT.[9–11,19,22,23] Radiotherapy may directly damage the thymic microenvironment that is necessary for the intrathymic maturation of thymocytes and may impair thymic function.[23] Aging is associated with thymic involution, which is accompanied by a decrease in thymic output.[8–11,19,22,24–26] Patients experiencing chronic GVHD are most vulnerable to opportunistic infections and have the most pronounced decrease in numbers and function of both B and T-cells.[27,28] This is in part explained by the immunosuppressive treatment for GVHD, but direct damage to the thymus and its function by GVHD is likely to be involved.[29–32] The latter is supported by the observation that patients with (extensive) chronic GVHD may have a hampered thymic output as measured by TREC analysis and by the production of a reduced number of $CD4^+$ T-cells.[11,19,33,34] Furthermore, GVHD is accompanied by thymic infiltration of activated allo-reactive T-cells, depletion of cortical and medullar thymocytes, epithelial cell damage and loss of Hassle's bodies in mice.[29–31,35–38] It results in impaired positive selection of newly developed T-cells as well as in impaired negative selection with the occurrence of autoreactive T-cells.[39,40]

Improving thymopoiesis after allogeneic SCT

Improving thymopoiesis may be an important way of improving T-cell recovery following allogeneic SCT. Strategies to improve thymic function may include approaches to protect the nursing stromal compartment and approaches to boost thymopoiesis by directly stimulating T-cell progenitors (Fig. 1).

Protection of thymic stroma

Protection of the thymic stromal compartment may be accomplished by the administration of cytokines that protect the thymic epithelium, such as keratinocyte growth factor (KGF) or growth hormone (GH). KGF or fibroblast growth factor 7 (FGF-7) was initially discovered as a stimulator of epithelial cell growth and is produced by mesenchymal cells and $\gamma\delta$ T-cells.[41–43] KGF is also produced by all thymocyte-subsets in the thymus and MHC II^+ CD45-thymic epithelial cells (TEC) express its receptor.[44,45] KGF may protect epithelial cells (which express the KGF receptor FGFF2IIIb) from damage by chemo- and radiotherapy[46–48] and GVHD.[44,49–51] Mice, pretreated with KGF, showed a reduced mortality rate from GHVD and less histological evidence of GVHD as compared to control mice following experimental BMT.[49,50] In addition, pretreatment with KGF may exert a long-term positive effect on thymic function in experimental murine BMT.[44,51] The mechanism by which KGF