Towards Individualized Conditioning Regimens to Improve the Outcomes of Cord Blood Transplantation

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Allogeneic Hematopoietic Cell Transplantation (HCT) is an important treatment option for a variety of malignant diseases and non-malignant disorders (NMD). The use of unrelated and alternative donors, including unrelated cord blood (CB) has made HCT available to many more patients. This has resulted in a dramatically changed life-perspective for patients with historically fatal disorders. The outcomes of HCT and CB-transplantation (CBT) is however highly variable among patients; understanding the sources of variability could significantly improve HCT outcome in terms of efficacy and tolerability of treatment. Relapse and transplantation-associated mortality (e.g. viral infections, GvHD) are the major limitations of HCT. The conditioning regimen given prior to HCT is one of the variables that may be optimized. Individualizing the conditioning regimen resulting in a predictable immune-reconstitution may significantly impact the outcomes.

In the conditioning regimen for HCT, a variety of cytostatic drugs (or TBI; total body irradiation) is combined with serotherapy (e.g. ATG; anti-thymocyte globulin; Thymoglobuline). It is hypothesized that the exposure to the drugs used in the conditioning phase is a major determinant of the variability in outcomes. This is even more prominent in pediatric patients due to an even more variable pharmo-kinetics for the various drugs used. For Busulfan, it has clearly been demonstrated that targeting to a predefined exposure and thereby reducing the variability in exposure substantially improves the outcomes: less graft-rejection, lower toxicity (e.g. VOD, aGvHD). More recent Fludarabine has replaced Cyclofosfamide since it has a more favorable efficacy-toxicity profile. Nowadays FluBu is used more and more as a conditioning platform in HCT including CBT. The drug having most significant impact on the immune-reconstitution after HCT/CBT is ATG (or other serotherapy: e.g. Campath). ATG is added to prevent “graft-versus-host disease (GvHD)” and rejection. ATG is a polyclonal antibody depleting T-cells having a long half-life. The therapeutic window is critical as over-exposure may result in delayed reconstitution of donor T-cells and increased risk of viral infections and relapse. We recently described the population pharmacokinetics (PK: Admiraal et al, Clinical Pharmacokinetics 2015) of Thymoglobulin as a first step towards an “evidence-based” dosing regimen of Thymoglobulin for HCT. Thereafter we did an extensive Pharmaco-dynamic analyses (n=251 pediatric patients, including 91 receiving a CBT. Only first HCT patients included; Admiraal et al, *The Lancet Hematology 2015*). In MV analyses the “overall survival” and “event free survival” were higher in patients with a low Thymoglobulin exposures after HCT ($p=0.0002$). Higher post-HCT ATG-exposure was associated with lower probability on T-cell reconstitution ($p<0.005$) which was most prominent in CBT recipients: even very low post-CBT ATG-exposure significantly hampered the immune-reconstitution. Interestingly, post-HCT (or CBT) exposure did not influence probability on aGvHD and cGvHD. Higher pre-HCT exposure however, was associated with a lower probability on aGvHD, cGvHD and graft-rejection. Poor immune-reconstitution was associated higher probability on viral infections (EBV, CMV, Adeno-virus and HHV6) and associated transplantation-associated mortality and relapse.

The conditioning regimen prior to HCT is an essential part of the HCT. PK and PD studies have taught us to optimize the outcomes of HCT. Individualizing the conditioning regimen may improve the outcomes of HCT due to a better predictable immune-reconstitution resulting in lower rates of virus-associated problems, relapse and higher survival chances. Furthermore a better predictable immune-reconstitution after CBT is of importance for the application of adjuvant immunotherapies after CBT; e.g. CARs, DC-vaccines and specific antigen CTLs.