

to support one over the others. We historically used CSA/MTX (n = 187 pts). Over the last 3 years we used CSA/MMF (n = 92). Median pt age was 52 years (18-73). Diagnoses included AML/MDS (n = 152), ALL (n = 30), CML (n = 12), myeloma (n = 24), lymphoma (n = 40), others (n = 21). The donor was 10/10 (n = 191), 9/10 (n = 54) or  $\leq$  8/10 match (n = 34). Conditioning was myeloablative (n = 58) or reduced intensity/toxicity (RIC, n = 221). Non-relapse mortality (NRM) is dependant on regimen toxicity and GVHD. CSA/MMF was less toxic than CSA/MTX. It allowed faster engraftment, day +11 and +14, respectively (p < 0.001). Day30 mortality was 2.2% and 10.7%, respectively (p = 0.04). Multivariate analysis (MVA) identified high comorbidity index (HR 2.5, p = 0.05), advanced disease (HR 6.2, p = 0.005), mismatched donor (HR 2.4, p = 0.03) and lymphoid malignancies (HR 2.8, p = 0.03) as adverse factors for regimen-related mortality. CSA/MMF was protective (HR 0.4, p = 0.02). However, CSA/MMF was less effective in preventing grade III-IV acute GVHD; cumulative incidence 29% and 18%, respectively (p = 0.005). MVA identified mismatched donor (HR 3.4, p = 0.001) and CSA/MMF (HR 2.4, p = 0.004) as adverse factors, while RIC was protective (HR 0.4, p = 0.01). The net effect was that NRM was equivalent with both regimens. GVHD regimen had major impact on overall survival (OS) when pts were stratified based on disease status. In early stage disease, OS was 65% and 42%, after CSA/MTX and CSA/MMF, respectively (HR 1.9, p = 0.05), predominantly due to excess GVHD deaths in the MMF group. In advanced disease, OS was better with CSA/MMF; 20% and 12%, respectively (HR 0.5, p = 0.04), predominantly due to less relapses. In conclusion, GVHD prevention regimen has major impact on outcome after MUD SCT. CSA/MMF is a less toxic regimen and allows prompt engraftment, but is less effective in preventing GVHD. In early stage disease, outcome is dominated by NRM and more effective GVHD prevention regimen such as CSA/MTX is needed. In advanced disease both toxicity and relapse increase. A less intensive regimen, that also better preserves GVL, such as CSA/MMF, may be associated with better outcome. The GVHD prevention regimen selected may need to be tailored to pt and disease characteristics.

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##### RITUXIMAB TREATMENT IN CHRONIC GVHD: CLINICAL EFFICACY ASSOCIATES WITH RESTORING A PHYSIOLOGICAL B-CELL BALANCE

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**Introduction:** Chronic graft-versus-host disease (cGVHD) is the major long term complication of allogeneic stem cell transplantation (allo-SCT). Although the contribution of donor T cells in the development of GVHD is beyond doubt, the role of B cells is less defined. Promising results of B-cell depleting therapy with rituximab (RTX), suggest that B cells do contribute to cGVHD. However, there is no consensus on the exact mechanism by which B cells can cause allo-reactivity.

**Objective:** In order to elucidate efficacy in a prospective clinical trial and elucidate the potential role of B cells in allo-reactivity and how B-cell depletion results in amelioration of steroid refractory extensive cGVHD, T- and B-cell subsets were studied before and after RTX treatment.

**Methods:** In a prospective phase I/II study 20 patients with steroid-refractory extensive cGVHD were treated with RTX (4 x 375 mg/m<sup>2</sup>). Clinical responses were monitored monthly for 1 year according to the NIH criteria. T-cell and B-cell subsets and phenotypes were analyzed before and after treatment in responders and non-responders and compared to time matched no GVHD controls (no GVHD) and healthy donors (HD) by FACS analysis. (EudraCT 2008-004125-42).

**Results:** A total of 80 RTX infusions were administered to 20 patients. Toxicity was limited to one infectious event and one allergic reaction. Median follow-up was 6.5 months (range 1-13). Overall response rate was 62%. Best clinical responses were observed in patients with deep sclerosis of the skin (80%). Before treatment absolute numbers of B cells were increased in responders compared to non-responders, no GVHD and HD. Moreover, selectively in responders also the balance within B-cell subsets was disturbed. One year after RTX treatment B-cells could be detected and responders had a restored physiological B-cell phenotype.

**Conclusion:** RTX treatment is a feasible and effective treatment in patients with steroid refractory cGVHD. Sclerotic lesions of the skin are most susceptible to treatment. In responders the increase in B cells before treatment and the disturbed phenotype suggest that a disbalance in B cells is involved in inducing cGVHD. This allows to speculate that cGVHD is heterogeneous and can be either B-cell or rather T-cell mediated. Analyzing B-cell numbers and phenotype in patients with cGVHD might be useful in upfront identification of patients which will benefit from RTX treatment and include patients which will not in alternative clinical trials.

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##### STANDARDIZED EARLY INITIATION OF A "HIGH DOSE STEROID (HDS)" TREATMENT PROTOCOL FOR ALLO-IMMUNE LUNG SYNDROMES IS ASSOCIATED WITH IMPROVED SURVIVAL DESPITE THE PRESENCE OF HIGH VIRAL LOADS OF "COMMON COLD VIRUSES"

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**Background:** Alloimmune lung syndromes (allo-LS), including Idiopathic Pneumonia Syndrome (IPS) and Bronchiolitis Obliterans (BOS), are severe life-threatening complications after HSCT. We recently found that a "common cold" respiratory viral (RV) infection early after HSCT is an important predictor for the development of allo-LS and that prolonged administration of immunosuppression, in patients with a RV infection, because of aGVHD, paradoxically had a protective effect on the development of allo-LS (BBMT 2010). We therefore hypothesised that despite presence of a RV, alloLD should be treated with 'high dose steroids (HDS)'. We prospectively studied the outcomes of the treatment of allo-immune lungsyndromes (alloLS) with a standard HDS-protocol" and compared this with our historical cohort.

**Methods:** All patients transplanted between January 2004 and July 2010, within our pediatric transplant program were included. All patients were tested for the presence of a RV using qPCR prior to HSCT and subsequently weekly till discharge. After discharge only when having symptoms. Allo-LS (IPS or BOS) was diagnosed according international criteria, excluding infection (except presence of a RV). In 2006 the HDS treatment protocol was introduced when allo-LS was suspected: MP-pulse (10mg/kg; 3 days), followed by 2mg/kg/d prednisone, tapered 25% per week till 0.5mg/kg. After 4 weeks the MP-pulse was repeated, followed by 0.5mg/kg/d for at least 1 months. In case there was still suspicion of disease the MP-pulse was repeated (max. 6times). Ciclosporine tough levels were maintained between 150 and 250 ug/L. In the old treatment guidelines we were reluctant giving HDS because of the presence of a RV.

**Results:** 182 patients were included of whom 38 (21%; 15% IPS and 6%BO) developed an allo-LS. 35/38 of the patients with an alloLS had a proven RV. Follow up: 36mths (1-76 mths). The overall survival was 63% (73% without alloLS, 43% with alloLS). Cause of death in the alloLS group was 90% TRM and 10% relapse. 10 pts were treated according to old treatment guidelines, while 28 were included in the HDS protocol. The probability of OS was 20% for the "old treatment group" while 54% of the patients within the HDS group survived (p = 0.041). The viral load of the RV, expressed as CT-values, remained stable (median value 20: range 17 - 24) during the treatment with HDS.

**In summary:** Early initiation of HDS in alloLS improved survival, despite the presence of a RV (infection).

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##### DISTINCT OLIGOCLONAL T CELLS ARE ASSOCIATED WITH GVHD OR GVHD-FREE RESPONSES IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES FOLLOWING STEM CELL TRANSPLANTATION

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Graft-versus-host disease (GVHD) and graft-versus-tumor (GVT) effects observed following allogeneic stem cell transplantation may be associated with unique clonal T cell expansion. To