Background: High dose busulfan (BU) has become a mainstay in conditioning regimens for hematopoietic stem cell transplantation (HSCT), despite its highly unpredictable response, narrow therapeutic index and severe toxicity. A steadily growing body of evidence indicates that the outcome of HSCT is highly dependent on population-specific genetic determinants.

Research Hypothesis: We hypothesize that response and toxicity associated with myeloablation by BU is determined by population-specific genetic variants.

Aims: The aim of this study was to assess the molecular basis of individualized outcome of myeloablation in Middle Eastern patients through ascertainment of known pharmacogenetic determinants in Israeli populations.

Methods: This study provides an integration of genetic, pharmacokinetic and clinical outcome data of patients preconditioned for HSCT with high dose BU. In addition, we present in vitro data on the effects of BU on T cells.

Results: The main findings of this study are as follows: (1) Adults diagnosed with AML carrying the GSTP1 variant allele (G) rs1695 are at risk of developing supra-therapeutic BU AUC due to lower BU clearance. (2) Combined polymorphisms in GSTM1 and ABCB1 are associated with BU clearance rates and AUC/F. (3) GSTA1 WT is under represented in AML patients who experienced disease relapse after HSCT. (4) MTHFR C677T ancestral allele (C) and A1298C variant allele (C) are significant risk factors for hepatic sinusoidal obstructive syndrome (SOS). MTHFR haplotype 677CC/1298CC appears to be significantly associated with SOS. (5) Disease relapse is not associated with BU pharmacokinetics. Microarray data identified significant networks, top functions and canonical pathways associated with the differentially expressed genes affected by BU. While still in early stages of analysis, it is obvious that BU affects multiple signaling cascades and cellular pathways. (6) BU significantly inhibits CD4+ and CD8+ T cell proliferation in a dose-dependent manner in vitro. The presence of monocytes does not affect BU-induced T cell proliferation inhibition. (7) BU causes cell cycle arrest in the G0/G1 stage, which cannot be reversed upon addition of IL-2, suggesting that the drug's mechanism of action does not involve anergy induction.

Conclusions: We believe that taken together, these results demonstrate the complexity of the molecular mechanisms underlying BU treatment outcome and suggest that better understanding of these cellular processes could lead to development of more potent treatment protocols for HSCT and possibly other hematological malignancies.

Key words: Busulfan, Pharmachogenetics, Pharmachokinetics, HSCT
Publications associated with the project:
