Karolinska Institutet

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TOXICOLOGICAL AND PHARMACOLOGICAL STUDIES OF BUSULPHAN, CYCLOPHOSPHAMIDE AND TREOSULFAN IN THE CONDITIONING REGIMEN PRIOR TO ALLOGENEIC STEM CELL TRANSPLANTATION

AKADEMISK AVHANDLING
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av

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ABSTRACT

Allogeneic stem cell transplantation (SCT) is a curative treatment for malignant and non-malignant diseases. However, transplantation related morbidity and mortality are major drawbacks affecting the survival and life quality of the patients. The major complications of SCT are infections, hemorrhagic cystitis, liver toxicity, interstitial pneumonia and GVHD. Busulphan (Bu), treosulfan (Tr) and cyclophosphamide (Cy) are alkylating agents. They are currently used in high doses as preparative regimen before SCT. Pharmacokinetics and pharmacodynamics of these drugs have been intensively studied with the aim of defining a therapeutic window to achieve a satisfactory myeloablation and immunosuppression with less treatment related toxicity.

Study I: We administered N-acetyl-L-cysteine (NAC) during conditioning to patients at risk of Sinusoidal obstructive Syndrome (SOS) due to pretransplant liver disorders or elevated liver enzymes. No side effects related to the NAC administration were observed and Bu-kinetics was not affected. All patients became pancytopenic and engrafted with100% donor cells. None of the patients developed SOS or liver failure. Increased liver enzymes during conditioning decreased or normalized in all patients. We suggested that NAC therapy is safe and does not impair the myeloablative effect of Bu during conditioning prior to SCT and hence NAC may be an effective prophylactic treatment against SOS and hepatic toxicity during conditioning.

Study II In a preclinical study, myeloablative as well as immunosuppressive properties of Tr were compared with those of Bu and Cy in a mouse model. The animals were treated with Tr, Cy, or Bu at sublethal doses that maintained survival without bone marrow support. The myeloablative effect was evaluated using colony-forming unit granulocyte macrophages (CFU-GM), while the immunological effect was studied using spleen cells. We found that Tr and Bu induced a high and persistent myeloablation compared to Cy. Moreover, Tr was more effective in depletion splenic B and T cells compared to Bu and Cy. T-cells isolated from the spleens of Tr- or Bu-treated mice were not responsive to allogeneic cells compared with those observed in Cy treated mice. Our findings suggested that Tr possesses both myeloablative and immunosuppressive properties and may be used as a single agent for conditioning prior to SCT.

Study III. Therapeutic drug monitoring (TDM) of Bu-iv was performed in 34 pediatric SCT patients. Bu-iv was administered twice daily according to recommended weight-based doses. Bu levels were measured and pharmacokinetic analysis was performed. The targeted Bu exposure was aimed to range between areas under the curve (AUC) of 9000–12000 ng/mLxh. In 23/34 patients (68%) Bu dose had to be adjusted at least once. In 16/23 patients the dose had to be increased in a range of 7-33%, while in 7/23 patients (30%) the dose had to be decreased by 7-20%. The need of dose adjustment was not related to weight, age or underlying disease. SOS was observed in 21% of the patients in spite of total AUC's within the target AUC. We concluded that TDM of iv Bu is essential to increase the efficacy and safety of Bu-based conditioning protocols in pediatric HSCT recipients.

Study IV. Limited sampling models for use in TDM of Bu in patients treated for hematologic malignancies. 23 patients were sampled according to standard protocol (8 samples). AUC calculated from three limited sampling models were compared with WinNonLin compartment modeling. Combining a curve fitting model and a compartment model, using the average AUC estimate, gave a intraclass correlation coefficient of 0.86 with the described standard sampling protocol. Using Bland-Altman plots it was evident that most patients would have been treated the same regarding dose adjustment using the combined method as well as standard rich sampling. The results support the use of limited sampling in clinical therapeutic drug monitoring, provided adequate algorithms are used for evaluation. Both models included in the combined method utilized four concentrations points. The model is reliable, solid and user friendly providing the clinician with a graph and a numeric AUC estimate.

These four studies taken together may provide a step forward in treatment optimization and dose individualization to the benefit of SCT patients.

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