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ACTUAL WEIGHT TO CALCULATE SURFACE AREA PROVIDES THE BEST ESTIMATE OF AUC FOR MELPHALAN IN MYELOMA

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High dose melphalan (MLP, 200 mg/m^2) is an important treatment for multiple myeloma, even in the era of novel biological agents. The prevalence of obesity is increasing, but there is little information on how best to adjust the dose in obese patients.

Aim: Use pharmacokinetic data from 16 lean patients (body mass index, BMI $\leq$ 25 kg/m^2) and 36 obese patients (BMI $\geq$ 30 kg/m^2) with normal renal function (est Cr Cl > 60 mL/min) to evaluate alternate size descriptors that best fit the actual drug exposure.

Methods: Plasma MLP levels were measured in 6-12 blood samples collected from 100 patients who had received a single high dose of MLP (median:192 mg/m^2). Individual results of MLP clearance were determined using a two compartment model developed using the NONMEM IV software. Subsequent analysis was restricted to obese and lean patients with normal renal function. Two-sided two-sample T-test was first used to compare MLP clearance of lean and obese patients. Extrapolating from individual clearance results, drug exposure (AUC) for obese patients (AUC_{obese}) was predicted using the formula dose/clearance, where dose was calculated either using actual body weight (ABW) in the formula for BSA or alternate weight descriptors. The AUC for lean patients (AUC_{lean}) used ABW in the BSA formula. The ratio of AUC_{obese}: mean AUC_{lean} was calculated and compared to unity (indicating equivalent exposure for obese and lean patients) using a two-sided, one-sample T-test. This analysis was repeated for each gender separately.

Results: MLP Clearance (L/h) is significantly higher in obese patients compared with lean patients (32.2 $\pm$ 10.2 versus 26.1 $\pm$ 6.2 L/h, $p < 0.05$), but after normalisation to BSA using ABW, there is no significant difference (15.9 $\pm$ 4.8 versus 15.2 $\pm$ 3.3 L/h/m^2). Using ABW in the BSA formula to determine dose, AUC_{obese} is (mean $\pm$ s.d.) 13.6 $\pm$ 3.9 mg/L.h, AUC_{lean} is 13.8 $\pm$ 2.9 mg/L.h, resulting in a ratio of 0.99 $\pm$ 0.29, which is not significantly different from 1.0. All other weight descriptors in the BSA formula (predicted normal weight, ideal body weight, adjusted ideal body weight, lean body mass and the mean of ideal and ABW) resulted in AUC ratios that were significantly lower than 1.0 ($p < 0.05$).

Conclusions: Use of ABW in the BSA formula to calculate dose rather than alternate weight descriptors achieves equivalent exposure to MLP in obese and lean patients. Continued follow up will assess the significance of these levels in all weight groups.

PEDIATRIC DISORDERS

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INTERNATIONAL MULTICENTER STUDY ANALYZING THE LONG TERM OUTCOME OF HURLER SYNDROME PATIENTS AFTER SUCCESSFUL HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Hurler syndrome (HS), the most severe phenotype in the spectrum of Mucopolysaccharidosis type I (MPS I), is caused by a severe deficiency of the lysosomal enzyme alpha-L-iduronidase (IDUA). HS is clinically characterized by a progressive and ultimately fatal multi-system deterioration with involvement of the central nervous system. At present, hematopoietic stem cell transplantation (HSCT) is the only treatment able to prevent disease progression in the central nervous system and therefore considered the treatment of choice in HS.

Successful donor engraftment in HS patients has shown to be highly effective, although with variable outcome between transplanted patients. Since long term follow-up data are sparse, insight in the long term outcome of successfully transplanted HS patients and the influencing factors are still largely unknown. Recently, an international multicenter study has been initiated analyzing the long term outcome of successfully transplanted HS patients worldwide. The primary outcome parameters consist of the neurocognitive/developmental and functional outcome. Secondary outcome parameters include the outcome regarding the various organ systems (eg orthopedic, cardiac, respiratory, ophthalmologic, etc) as well as the quality of life and processes of care. This international study will include 'alive and engrafted' HS patients, with a follow up of at least three years post-HSCT. These patients, approximately 200 (about 80% of the HS patients successfully transplanted worldwide), have been transplanted between 1980 and 2006 at the leading transplantation centers in Europe as well as the United States. From eight centers, with a total of 160 patients by the end of 2009, data collection is already achieved. An update of the study will be presented during the meeting.

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OUTCOMES OF TRANSPLANTATION USING A VARIOUS CELL SOURCE IN CHILDREN WITH HURLERS SYNDROME AFTER MYELO-ABLATIVE CONDITIONING. AN EUROCORD-EBMT-CIBMTR COLLABORATIVE STUDY

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Hurlers syndrome (HS), the most severe form of mucopolysaccharidosis type-I causes progressive deterioration of the central nervous system and death in childhood. Allogeneic-stem cell transplantation (SCT), if performed early halts disease progression and prolongs life. Graft-failure and mixed-chimerism (40-50%) limit the success of SCT in HS. Various cell sources including unrelated cord blood have been used over the last decades. However, impact of various cell sources (Matched Sibling donor; MSD, unrelated donor; UD, unrelated cord blood; uCB and T-cell depleted UD; TCDud) on outcomes of SCT in HS is not well studied. We have analyzed 258 HS children that received a SCT after a myelo-ablative conditioning regimen from 1995 to 2007 and were reported to EUROCORD, EBMT or CIBMTR. Median age at SCT was 16.7 (2-228) months, and median follow up was 57 (1.3-140) months. The donors were MSD (n = 37; 14%), UD (n = 52; 21%), uCB (n = 116; 44%), TCDud (n = 53; 21%). All but 8 patients, received a Busulfan-based myeloablative regimen. All patients receiving an unrelated donor and 8 MSD received ATG (n = 207) or Campath (n = 21).

Overall neutrophil recovery was 91+/-3% at day 60. Overall acute-GvHD (grade II-IV) was observed in 26%, while chronic-GvHD was seen in 12+/-3% at 5 years. Five years overall survival (OS) and disease and event free survival (EFS) were 74% and 64%, respectively. For OS at 5 years, an age of <20months at SCT was associated with a higher survival (p = 0,04). OS was higher after MSD (92%), compared to the other sources UD (76%; p = 0.078), uCB (74%; p = 0,038) and TCDud (64%; p = 0,007). EFS at 5 years was similar between MSD (81%), MUD (69%; p = 0,148) and uCB (67%; p = 0,11) but lower after TCDud (38%; $p < 0.001$). Of those who