Poster

[P26-9] P26-9: Oncologic drugs (5): Pharmacokinetics, TDM practice

Chair: Kiyoshi Mihara, Japan

Tue. Sep 26, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Tue. Sep 26, 2017 12:30 PM - 1:30 PM Annex Hall)

[P26-9-2] Pharmacokinetics of plasma busulfan using isotope dilution mass spectrometry: a pilot study of patients receiving hematopoietic cell transplant in Taiwan

Wei-Chi Ku[1], Li-Hua Fang[2], Xin-Yi Yang[3], Rong-Long Chen[4], Wen-Hui Ku[5], Yen-Fu Chen[6], Erik van Maarseveen[7] (1.Fu Jen Catholic University, 2.Koo Foundation Sun Yat-Sen Cancer Center, 3.Koo Foundation Sun Yat-Sen Cancer Center, 4.Koo Foundation Sun Yat-Sen Cancer Center, 5.Taipei Institute of Pathology, 6.Fu Jen Catholic University, 7.University Medical Center Utrecht)

Keywords: busulfan, hematopoietic stem transplantation, TDM-guided dosing

Background

Busulfan, a corner stone of conditioning prior to hematopoietic stem transplantation (HCT), has been used since the 1950s and has a narrow therapeutic window. Therapeutic drug monitoring (TDM)-guided dosing of intravenous busulfan AUC with a target of 78 - 101 mg x h/L has been shown to reduce graft failure and relapse rate (Bartelink, et al., *Lancet Haematol* 2016, 3, e526-e536). However, TDM of busulfan for patients receiving HCT has not been applied in Taiwan. Therefore, we conducted a pilot study of busulfan TDM to assess the optimal dosing of busulfan in Taiwanese population.

Methods

Busulfan was administered once daily as a 3-hour infusion on 4 consecutive days. Plasma samples were drawn at 5 min, 1 hr, 2 hr, and 3 hr after the end of busulfan infusion on day 1 and day 4. Plasma samples were analyzed at Fu Jen Catholic University (FJCU), Taiwan and UMC Utrecht, the Netherlands using liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods with a Thermo Scientific TSQ Quantiva Triple Quadrupole Mass Spectrometer in both instances. Busulfan exposure in individual patients were calculated on both sites as cumulative area under the concentration-time curve (cAUC) using a Bayesian fitting procedure with PK Software (MW Pharm, Mediware, Zuidhoorn, the Netherlands) and a PK model. The accuracy and precision of the dosing nomogram was assessed on model prediction (90 mg x h/L) with TDM cAUC was determined on PK data on day 1, including dose adjustment based by UMC Utrecht lab data report.

Results

Method validation for plasma busulfan quantification at FJCU proved linear within a range of 400 –6400 μg/L (r^2 = 0.99). The average CV’ s of low, med and high QC were all within 10%. Next the plasma sample from 6 consecutive HCT patients (age from 3 months to 56 year) were analyzed included between year 2015 and 2016. In order to check our data in FJCU, we compared independent cAUC data of FJCU to those obtained at UMC Utrecht, and the difference of cAUC ranged between -15% to 6%. In addition, 5 patients (83%) were needed dose adjustment based on the target AUC. All patients had engraftment without development of sinusoidal obstruction syndrome.

Conclusions

This pilot study describes the first busulfan TDM experience in Taiwan, and demonstrates a robust TDM

procedure when compared to the results from a reference center. Optimal busulfan AUC targets and the contribution of TDM to improve patient outcomes deserve further investigation in the Taiwanese population.