Poster

[P26-7] P26-7: Oncologic drugs (3): Pharmaometrics, PK/PD, special population

Chair: Shiro Fukumori, Japan

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[P26-7-10] High exposure to fludarabine in conditioning prior to allogeneic hematopoietic cell transplantation predicts impaired CD4 reconstitution and lower probability of survival

Erik van Maarseveen[1], Jurgen Langenhorst[2], Charlotte van Kesteren[3], Thomas Dorlo[4], Stefan Nierkens[5], Jurgen Kuball[6], Moniek de Witte[7], Alwin Huitema[8], JaapJan Boelens[9] (1.University Medical Center Utrecht, 2.University Medical Center Utrecht, 3.University Medical Center Utrecht, 4.Antoni van Leeuwenhoek Hospital/Netherlands Cancer Institute
, 5.University Medical Center Utrecht, 6.University Medical Center Utrecht, 7.University Medical Center Utrecht, 8.University Medical Center Utrecht, Antoni van Leeuwenhoek Hospital/Netherlands Cancer Institute, 9.University Medical Center Utrecht)

Keywords: Fludarabine exposure, CD4+ T-cell reconstitution, Overall survival

Background

Fludarabine (Flu) is widely used in conditioning prior to allogeneic hematopoietic cell transplantation (HCT) in combination with busulfan (Bu). Whilst targeting Bu to optimal exposure has been shown to increase survival, to date there is no optimal exposure known for Flu. As Flu has strong cytotoxic and immunosuppressive properties, this study aims to relate Flu exposures with CD4 T-cell reconstitution (IR) and overall survival (OS).

Methods

In this retrospective single-center study, the circulating metabolite of Flu (F-ara-A) was quantified in samples acquired for routine Bu therapeutic drug monitoring (TDM, from 2010) using a validated liquid chromatography mass spectrometry method. With these data, a pharmacokinetic model was developed and cumulative Flu area under the curve (AUC) was determined.
Main outcomes of interest were OS and IR. A value of 50 million CD4+ T-cells per liter was chosen as dichotomous measure for IR. The time point at which a patient had the second consecutive measurement above threshold was defined as time of IR. Statistical analyses were done using Kaplan-Meier estimation and parametric time-to-event (TTE) models.

Results

For the outcome analyses 159 patients were included (100 adults, 59 children) treated for a variety of malignant (n=105) and benign disorders (n=54), with a median age of 38 years (range 0.23-74).
To find an optimal cut-off, Flu exposure was assessed as a biomarker for survival using receiver-operating characteristic curves. A cut-off of 21.6 mg*h/L was found to be optimal, resulting in a significant difference in survival: 40% OS above and 67% below this cut-off. ($p<0.001$: figure 1).
The exposure cut-off was tested in the TTE model and remained predictive for survival: HR 2.3, 95% CI 1.3 - 4.5, p=0.009. (covariates: age and indication) Flu AUC continuously impaired IR in the TTE model from 0 to the maximum AUC of 49.1 mg*h/l. (OR 0.11, p=0.005)

Conclusions

High exposure to Flu impairs CD4+ T-cell reconstitution and reduces survival after HCT.
This is the first step in the definition of a target exposure for Flu in this setting. Dose individualization and/or TDM-based corrections towards the Flu target is warranted to reduce overexposure and improve survival after HCT.

Zoom image

Figure 1: Overall survival after HCT for patients with Flu exposure above and below cut-off value. Lines depict Kaplan-Meier estimates corresponding to the different groups. Percentages displayed are estimated 2-year OS and 95% confidence interval at 2 years. P-value is calculated using log-rank test.