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A NOVEL INTEGRATIVE MULTI-OMICS APPROACH TO UNRAVEL THE GENETIC DETERMINANTS OF RARE DISEASES WITH APPLICATION IN PEDIATRIC SINUSOIDAL OBSTRUCTION SYNDROME

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Background: Genotype-phenotype association analyses of rare diseases often suffer from a lack of power, due to small sample size, which makes identifying significant associations difficult. Furthermore, failure to adjust for genetic heterogeneity in the population sample can lead to spurious findings. Here, we present a novel pipeline to address these issues and perform an analysis in sinusoidal obstruction syndrome (SOS), a life-threatening complication in hematopoietic stem cell transplantation (HSCT), particularly among children.

Methods: First, we investigated in vitro gene expression changes in lymphoblastoid cell lines (LCLs) after treatment with busulfan, a drug closely associated with SOS. Second, we applied several filtering steps on whole-exome sequencing (WES) data from 87 pediatric HSCT patients, treated with busulfan, to reduce genetic heterogeneity in the sample. Third, we used these filtered WES data to conduct an association analysis with SOS, at the SNP and the gene levels. Fourth, we computed a combined gene-based test statistic, and its associated p-value, by integrating the results of the in vitro differential gene expression analysis and the gene-based test for clinical association. By integrating the expression and association data at the gene level, we increased the power to detect genetic determinants of the clinical outcome of interest, since the resolution of our approach is expected to be higher than (i) a classical exome-wide analysis, as we combine evidence from independent experiments, and (ii) a candidate gene study, as we don't focus exclusively on a few candidates, selected a priori. Finally, we used an over-representation analysis and data from the Reactome database to functionally characterize the genes that were associated with a significant combined test statistic.

Results: After treatment of LCLs with busulfan, 1708 genes were significantly up-, and 1385 down-regulated, after the application of the Benjamini-Hochberg correction for multiple testing. Using WES data from 87 children with 12 SOS patients and 75 controls, we found 7 SNPs and 4 genes (*E2F4, MIR34C, NACAP1, and SHCBP1*) to be significantly associated with SOS in children, after Bonferroni adjustment for multiple testing. The combination of the expression experiment and the association analysis of WES data into a single test statistic identified 35 genes significantly associated with the outcome, after Bonferroni correction (AFAP1L2, AIM1, ANKRA2, CALML6, CCND1, CLCF1, DDR1, DDX60, FAS, GAS7, GBP5, GNA15, GPR137B, HCAR3, HSPG2, IL17RC, ITGAM, ITGB8, LACC1, LINC01021, MAP4K4, MDM2, PADI4, PGAP1, PHYHIP, POLH, PPL, PTP4A1, SEMA6A, TMEM168, TNFRSF10B, TRIM55, TRPV3, UTRN, ZBTB7C). These genes are involved in various pathways which are associated with cell growth and death, signaling molecules, and endothelial cell functions.

Conclusions: We presented here a novel data analysis pipeline which integrates two independent omics datasets and increases statistical power for identifying genotype-phenotype associations. The analysis of the in vitro transcriptomics profile of cell lines treated with busulfan and clinical WES data from HSCT patients

allowed us to identify potential genetic contributors to SOS. Our pipeline could be useful for identifying genetic contributors to other rare diseases especially in pediatrics where limited power renders genome-wide analyses unpromising.

Disclosure: We have no conflicts of interest to disclose.

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WMDA'S GLOBAL TRENDS REPORT ON UNRELATED HEMATOPOIETIC STEM CELL DONATION: 25 YEARS OF MONITORING ACTIVITY AND TRENDS

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Background: Hematopoietic stem cell transplantation (HSCT) is an established therapy for disorders of the hematopoietic system. An estimated 1.5 million recipients have undergone this procedure, giving a new chance of life to patients with otherwise incurable diseases. Approximately 250.000 of these recipients received stem cells from an unrelated donor (UD) or cord blood unit (CBU). A key project of World Marrow Donor Association (WMDA) is the Global Trends Report (GTR) which has become an established instrument to describe the global status of hematopoietic stem cell (HSC) donation by UDs and CBUs.

Methods: UD and CBU organisations worldwide are requested to report annual data in the WMDA GTR, which was first conducted and published to the WMDA community in 1997. Initially it was designed as a simple excel sheet, and over the years has been adapted and expanded to reflect the developments in the field. Since 2014 the data is collected through an online questionnaire which organisations can access through a secured website with their organisation's account, feeding the data into a central database. Quality control measures include validity cross checks within the GTR system as well as crosschecks between years by WMDA staff. Approximately 95% of organisations respond to the request to submit data, the unresponsive 5% mostly are organisations starting or stopping their activities. This report, based on the 2021 GTR, shows growth of the global database, changes in use of stem cell type, and summarizes the last 25 years.

Results: Numbers of global registered HSC donors and subsequent donations continued to rise to 41,134,730 UDs and 837,161 CBUs available for HSCT and 24,397 HSC donations shipped worldwide (2,857 marrow, 18,956 apheresis and 2,584 CBU) reported by 99 organisations in 56 different countries in 2021. Compared to 1997, where 36 organisations from 33 countries reported 4,766,411 UDs and 2,929 CBUs available for HSCT and 3,160 HSC products shipped globally (3,033 marrow, 113 apheresis and 14 CBU). The largest number of UDs and CBUs available for HSCT are registered in Europe and North America ((table 1). The activity has expanded immensely in the last 25 years, especially since global HSCT activity in 2021 was still negatively influenced by the COVID-19 pandemic.

Conclusions: The WMDA GTR system and commitment of participating UD/CBU organisations allowed WMDA to observe trends in HSC donation over 25 years and apply that knowledge into developing recommendations and describing standardised practice to advance the field and help ensure the safety of donors and patients.

In addition to the expansion of the global inventory of available UDs/CBUs throughout all continents, most notable developments include the increased use of apheresis over bone marrow as primary method for obtaining HSC, and the increase followed by decrease in number of CBUs banked and donated for HSCT. In the coming years it will be vital to monitor the recent rise in cellular therapy.

Looking at the distribution of available UDs/CBUs over the continents, diversity of registered UDs/CBUs should be improved to ensure equal access for all patients in need of a HSCT.

Disclosure: Nothing to declare.

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AUTOLOGOUS PERIPHERAL BLOOD STEM CELL PROCESSING IN KAUNAS, LITHUANIA 2015-2022

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Background: Peripheral blood stem cells (PBSCs) are widely used for autologous blood stem cell transplantation (auto-SCT) for patients with various conditions. CD34+ cell viability evaluation after cryopreservation and thawing is an important parameter used for quality assurance of the cryopreserved cells. CD34+ cell post-thaw viability results and their correlation with clinical parameters were evaluated.

Methods: The study included 209 patients, 461 aphereses, 640 products and 239 auto-SCT in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics from 2015 to 2022 December. The patient's plasma and DMSO (final concentration 10%) were used for PBSC cryopreservation. PBSC products were cryopreserved using a controlled freezer and then transferred to vapor phase nitrogen. Cell viability was evaluated after thawing PBSC in a water bath at 37 °C. Immediately after thawing viability was assessed using a BD FACS Canto flow cytometer and BD Stem Cell Enumeration Kit. A linear regression model and Pearson correlation were used for statistical analysis. The study included 209 patients, 461 aphereses, 640 products and 239 auto-SCT in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics from 2015 to 2022 December. The patient's plasma and DMSO (final concentration 10%) were used for PBSC cryopreservation. PBSC products were cryopreserved using a controlled freezer and then transferred to vapor phase nitrogen. Cell viability was evaluated after thawing PBSC in a water bath at 37 °C. Immediately after thawing viability was assessed using a BD FACS Canto flow cytometer and BD Stem Cell Enumeration Kit. A linear regression model and Pearson correlation were used for statistical analysis.

Results: In total 209 patients (106 females and 103 males) with a median age of 59 (range 18–73) years were harvested after G-CSF (10g/kg) or Cyclo+G-CSF or additional mobilizing agents such as plerixafor (0.24 mg/kg) for auto-SCT. The median post-thaw $CD34^+$ viability was 75% (range 1–96). Median leukocytes ($>1.0 \times 10^9$/l) engraftment on two consecutive days was 11 (range 8–13) days, and 15 days for platelets ($>50 \times 10^9$/l), ranging 9–23 days after SCT. Statistically significant negative correlations were observed between $CD34^+$ cell post-thaw viability and $CD45^+$ count in leukapheresis product ($p = 0.001$, $R^2 = 0{,}076$); $CD34^+$ count ($p = 0.002$, $R^2 = 0.02$); a volume of leukapheresis product ($p = 0.001$, $R^2 = 0.076$).

Conclusions: The results suggest that cryopreservation of cells using 10% DMSO final concentration is acceptable with successful cell engraftment in all patients. Lower CD45+ and CD34+ cell counts and lower leukapheresis volume had a better impact on

UDs registered per continent	1997	2005	2013	2021	Fold increase 1997-2021	Continent population (2020)[a]	UDs registered 2021/1 million inhabitants	% of population registered UD 2021
Africa	1,168	58,838	66,040	95,206	82	1,340,598,147	71	0.01%
Asia	321,290	1,374,534	4,195,922	7,792,679	24	3,261,050,390	2,390	0.24%
Europe	1,737,453	4,357,411	8,461,066	17,627,545	10	747,636,026	23,578	2.36%
North America	2,592,098	4,624,125	7,955,640	9,914,556	4	592,072,212	16,746	1.67%
Oceania	114,402	162,068	186,361	188,574	2	43,111,704	4,374	0.44%
South America	0	153,736	3,252,697	5,516,170	36	430,759,766	12,806	1.28%
CBUs banked per continent	1997	2005	2013	2021	Fold increase 1997-2021	Continent population (2020)[a]	CBUs banked 2021/1 million inhabitants	% of population banked CBU 2021
Africa	0	0	0	0	NA	1,340,598,147	NA	NA
Asia	298	57,060	178,105	219,560	737	3,261,050,390	67	0.01%
Europe	1,759	86,276	234,837	275,340	157	747,636,026	368	0.04%
North America	872	124,355	270,752	283,362	325	592,072,212	479	0.05%
Oceania	0	14,836	27,624	37,981	3	43,111,704	881	0.09%
South America	0	435	12,852	20,918	48	430,759,766	49	0.00%

[a]via worldometer.info. *UD* unrelated donor; *CBU* cord blood unit; *NA* not applicable.

post-thaw cell viability. Further studies are needed to confirm these findings and improve post-thaw cell viability.

Disclosure: Study authors declare no conflict of interest.

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USING R SCRIPTS VISUAL IN POWER BUSINESS INTELLIGENCE TO CREATE DASHBOARD FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION AND CELLULAR THERAPY CENTERS

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Background: Hematopoietic stem cell transplantation and cellular therapy (HSCT/CT) are treatments for many diseases. The data registry for HSCT/CT are important to scientific production and outcomes analysis. The Center for International Blood & Marrow Transplant Research (CIBMTR) is a registry which collaborates with the global scientific community to advance HSCT and other CT worldwide to increase survival and enrich quality of life for patients. Brazilian centers submit data on HSCT/CT performed at their institution in the CIBMTR. The Data Back to Center (DBtC) is a CIBMTR tool that allows centers to extract their data in a standardized and codified way. Through this extracted data it is possible to know some outcomes of HSCT/CT. However, to understand results is a difficult task without the use of advanced technological resources.

Objective: To demonstrate the development of a dashboard through statistical analysis using R script visual in Power Business Intelligence (PBI) with multicenter sharing.

Table 1. R script for survival analyses and risk table

```
library(survival)
library(ggplot2)
library(survminer)
require("survival")

fit <- survfit(Surv(Surv, Status) ~ AdultPed,
data = dataset)
ggsurvplot(
fit,
data = dataset,
size = 1,                                  # change line size
xlab = "Time (Years)",
palette = c("#E7B800", "#2E9FDF"),         # custom color palettes
conf.int = FALSE,                          # Add confidence interval
pval = TRUE,                               # Add p-value
risk.table = TRUE,                         # Add risk table
risk.table.col = "strata",                 # Risk table color by groups
legend.title = "Type",
risk.table.height = 0.25,                  # Useful to change when you have multiple groups
ggtheme = theme_bw()                       # Change ggplot2 theme
```

Methods: Data for analysis from a developer center were extracted through the DBtC, with information from transplants performed from 2008 to 2022. The data extracted from DBtC were imported into PBI. Functions were created to remove spaces from field names; to categorize and to group disease status prior to transplant for acute leukemia diagnosis (1st complete remission, >= 2nd complete remission and relapse/never in remission); to convert status indicator (censor = 0, event = 1). Filters were also created by disease, disease status prior transplant, transplant year and adult/pediatric classification. Power BI does not have an innate survival plot built in, thus it was added an R script visual to the dashboard in PBI. The code for survival analyses and risk table was created through the R script editor using survminer, survival and ggplot2 packages (table 1). For sharing the dashboard with a guest center which did not have a PBI pro licence, the developer center created a guest account using Microsoft Azure. The guest center saved your extracted data in the OneDrive and sent the link with the file path to the developer center. The link was configured in the PBI as parameter and the dashboard was published.

Results: It was possible to develop a dashboard through statistical analysis using R script in PBI. The dashboard was

published and shared between two centers from different organizations. Each center visualized a dashboard with its own data extracted through the DBtC.

Conclusions: The work using the R script in PBI allows the creation of some statistical analysis with data extracted from the DBtC, allowing to know results about acute leukemia disease according some categories. It was possible *p* value analysis among groups. But to publish dashboard it's necessary PBI pro license. Among the advantages of using PBI pro in this study, we assume that, once the dashboard has been developed and published, it creates the possibility to share dashboards with other centers which belong to other university hospitals, even with multiple and partners, without the need of making new analysis.

Disclosure: Nothing to declare.