Paper # 2009

MTHFR POLYMORPHISMS ARE ASSOCIATED WITH DECREASED METHOTREXATE TOLERANCE IN PEDIATRIC ALL

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Background: Methotrexate (MTX) forms a critical component in the treatment of pediatric acute lymphoblastic leukemia (ALL). MTX, through its action on the folate metabolic pathway, interferes with DNA and protein synthesis, thereby exerting it's antileukemic effects. MTHFR is an enzyme that serves as the rate limiting step within this pathway and there is evidence that certain MTHFR single nucleotide polymorphisms alter physiologic responses to MTX, including drug toxicity.

Objectives: To assess the effect of MTHFR genotype on tolerance to MTX.

Design/Method: We performed a retrospective analysis of pediatric patients treated at our institution from January 2012 to March 2021 to assess correlation between different MTHFR genotypes and MTX induced toxicities. We examined tolerance to MTX, specifically maximum tolerated oral MTX doses during maintenance, maximum tolerated Capizzi MTX (C-MTX), and MTX clearance times during high dose MTX (HDMTX). We also examined the frequency MTX-associated toxicities.

Results: Within our study population, 47 out of 242 patients were tested for MTHFR SNPs, with 33/47 demonstrating the commonly studied polymorphisms, C677T and A1298C. Of these, 9 were heterozygous for the C677T polymorphism, 9 were homozygous for the C677T polymorphism, 6 were heterozygous for the A1298C polymorphism, none were homozygous for the A1298C polymorphism, and 9 were heterozygous for both the C677T and A1298C polymorphisms. Patients with MTHFR genotypes including homozygous C677T and compound heterozygous C677T/A1298C demonstrated significantly decreased tolerance to oral MTX as demonstrated by decreased maximum tolerated MTX dosing relative to control (11.9 ± 9.5 vs. 19.9 ± 7.5 mg/m^2, $p < 0.05$ and 11.4 ± 6.1 vs. 19.9 ± 7.5 mg/m^2, $p < 0.01$, respectively). In contrast to this observation, only patients with the homozygous C677T genotype showed significantly decreased tolerance to C-MTX (174 ± 89 vs. 285 ± 90 mg/m^2, $p<0.05$). There were no genotypes associated with lengthening or shortening of clearance times in response to HDMTX. Clinically significant MTHFR genotypes were likely to be detected in the presence of myelosuppression (OR= 5.4, 95% CI 1.3-17.5, $p< 0.02$), but no other known MTX adverse effects demonstrated predictive ability. Lastly, no genotypes were associated with increased risk of developing MTX leukoencephalopathy or thrombosis.

Conclusion: MTHFR genotypes including homozygous C677T and compound heterozygous C677T/A1298C are associated with decreased tolerance to MTX and increased myelosuppression. Further exploration is needed to determine if reduced dosing of MTX is warranted to minimize toxicity.

Paper # 2010

REAL-WORLD OUTCOMES FOR PEDIATRIC PATIENTS AGED <3 YEARS WITH R/R ALL TREATED WITH TISAGENLECLEUCEL

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Background: Real-world outcomes with tisagenlecleucel in children and young adults with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL) are similar to those observed in clinical trials (John, Blood, 2021; Pasquini, Blood Adv, 2020). Although patients <3 years of age were excluded from clinical trials, successful leukapheresis and manufacturing have been demonstrated in this age group (Willert, Blood, 2021). Real-world clinical outcomes for these patients are reported here.

Objectives: Report clinical outcomes from the CIBMTR registry for patients <3 years at time of request for tisagenlecleucel.

Design/Method: Patients received tisagenlecleucel in the USA after August 30, 2017. Efficacy and safety were assessed at each reporting center in patients with ≥3 months' follow-up. Efficacy outcomes included complete response (CR), duration of response (DOR), event-free survival (EFS) and relapse-free survival (RFS). Adverse events of interest included cytokine release syndrome (CRS), neurotoxicity and infections.

Results: As of September 8, 2021, 47 patients were infused, with median age 20.4 months (median age at diagnosis: 6.7 months; 51.1% female; median weight: 10.3 kg). Indication was primary refractory disease in 17% of patients; relapsed in 57.4%. Pre-infusion, disease status was morphologic CR in 25.5% (19.1% MRD-negative). 34.0% of patients had ≥5% bone marrow blasts; 78.7%, *KMT2A*-rearrangement; no patients had Down syndrome. Prior treatment included alloSCT (19.1%), blinatumomab (12.8%) and inotuzumab (6.4%). Most patients (78.7%) were transplant-naïve.
Median age at leukapheresis was 18 months (range, 3–35; N=44, 3 patients with missing data); median, 1 day of leukapheresis. There was one manufacturing failure, which was successful upon repeat. Median dose, $2.4x10^6$/kg CAR+ T-cells; viability 89.8%. Median time from apheresis to infusion: 46 days (diagnosis to infusion: 251).

In the efficacy set (N=38; median follow-up: 23.8 months), 76.3% of patients had CR within 100 days. Three-month DOR and RFS were 79.9% (median not reached for either); EFS, 65.2% (median 9.7 months).

In the safety set (N=41; median follow-up: 23.1 months), 63.4% experienced CRS within 100 days (Grade ≥3: 7.3%; median time to onset: 6.5 days; median duration: 6 days) and 12.2%

neurotoxicity (7.3%; 9 days; 8 days). Three patients experienced seizures. All neurotoxicity resolved. Clinically significant infections within 100 days were reported in 39.0%. Two deaths were reported within 30 days, both due to progressive disease.

Conclusion: Registry data reveal high rates of durable response and a favorable safety profile in patients <3 years with R/R ALL treated with tisagenlecleucel. Data stratified by age and body weight will be presented.

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Paper # 2011

SCD25 AND FERRITIN LEVELS BEST DISTINGUISH CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome that is caused by underlying genetic defects or occurs secondary to triggers which lead to a distinct constellation of features. Current diagnostic criteria are based on enrollment criteria established for the HLH-2004 clinical study despite their unknown sensitivity or specificity. Both delayed diagnosis and misdiagnosis can be detrimental to patient outcomes.

Objectives: Validate the discriminatory power of the HLH-2004 parameters using a large cohort of curated controls and patients with confirmed HLH.

Design/Method: We gathered a cohort of control patients with HLH features and compared it to a cohort of patients with confirmed HLH (fulfilling ≥5 HLH-2004 diagnostic criteria or a known genetic defect). Controls included patients younger than 21 years without diagnosis of HLH or leukemia, and in whom a CBC, ferritin, and one additional HLH-related parameter was obtained within a narrow time window at Cincinnati Children’s Hospital from 2010-2020. Peak/nadir values from a range of clinical and laboratory parameters obtained within 14 days of presentation were assessed. Patients presenting with fever were defined as intermediate pretest probability controls. Patients who had soluble CD25 (sCD25, sILR2a) levels examined were defined as high pretest probability controls. Peak values were compared to peak baseline values in patients treated for HLH.Receiver-operating curves were used to identify the most useful diagnostic parameters. Cutoff points were derived from the highest Youden-index point. Results were validated using patients with known genetic defects, the gold standard for diagnosis.

Results: We identified 18,204 potential controls, 907 intermediate pretest probability controls, and 321 high pretest probability controls. Hemoglobin, platelet count, absolute neutrophil count, sCD25, ferritin, triglycerides, and fibrinogen showed significant discriminatory ability (area under the curve (AUC) ≥0.7) between the HLH cohort and both control groups. The individual parameters with the greatest discriminatory power were sCD25 (AUC of 0.89) and ferritin (AUC

of 0.95 when compared to intermediate pretest probability controls and 0.94 when compared to high pretest probability controls). Discriminatory ability further improved with a combined elevation of sCD25 and ferritin (AUC 0.96). Optimized thresholds of sCD25 and ferritin were higher than HLH-2004 cutoffs in each analysis. Moreover, when comparing controls to genetically diagnosed patients, sCD25 had the highest discriminatory power with an AUC of 0.96 and with ferritin, a combined AUC of 0.98.

Conclusion: Of the current HLH-2004 criteria, sCD25 and ferritin are the strongest individual diagnostic markers. Diagnostic power further improves with combined elevation and higher, optimized threshold values.

Paper # 2012

THE IMPACT OF TIME-TO-ANTIBIOTIC DELIVERY IN PEDIATRIC CANCER PATIENTS WITH FEBRILE NEUTROPENIA

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Background: Time-to-antibiotic (TTA) is defined as the time between patient presentation to a medical center with febrile neutropenia (FN) and any intravenous antibiotic administration. A TTA benchmark of <60 minutes is a metric set by U.S. News and World report, and compliance directly impacts pediatric oncology program rankings. Seeking to meet this metric has the potential for inferior care including inappropriate choice of antibiotics for severely neutropenic patients and use of painful intramuscular injections.

Objectives: To assess whether shorter TTA leads to fewer adverse outcomes in pediatric cancer patients with FN.

Design/Method: Pediatric cancer patients diagnosed 2006-2013 at a single institution were identified, and episodes of severe FN were abstracted. Inclusion criteria for FN episodes included fever (≥38.0°C), central line presence, not already on intravenous antibiotics, and an absolute neutrophil count (ANC) <500 cells/µl. TTA was evaluated both as a continuous variable and nominally (over/under 60 minutes). Continuous variables were compared using Wilcoxon Rank Sum test, and nominal variables were compared using Pearson's Chi square/Fisher's exact test. Primary outcomes included intensive care unit (ICU) admission, vasopressor support, death, length of hospital stay, need for bolus intravenous fluids (by 6 or 24 hours), or new oxygen requirement.

Results: Of 706 FN episodes, 4 (0.6%) required immediate ICU admission at presentation with a median TTA of 18 minutes (range 11-25 minutes). The remaining 702 episodes had a median TTA of 68.5 minutes (interquartile range [IQR] 46-106, range 4-793), and 39.7% were given antibiotics in <60 minutes. ICU care was required ≤6 hours in 0.6%, ≤24 hours in 2.1%, and ≤7 days in 3.3%. Continuous and nominal TTA were not associated with ICU admission at any

time, and ICU patients had shorter TTA at all time points. Vasopressor support within 7 days occurred in 2.4%. TTA was shorter in the vasopressor group (61 vs. 69 minutes), and vasopressor support was not associated with TTA. Mortality during the FN episode occurred in 0.6%. TTA was shorter for those who died (median 51.5 vs. 69 minutes), and mortality was not associated with TTA. Length of stay, bolus intravenous fluid administration, and new oxygen requirement within 7 days were also not associated with TTA. Blood stream infections occurred in 17%, and when assessing all outcomes in this population, there were no associations with TTA.

Conclusion: We did not observe that shorter TTA, particularly at the 60-minute timepoint, improves clinical outcomes. Alternative metrics are instead needed to better define quality of care.