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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Pre-Transplant Measurable Residual Disease (MRD) Detection of *KMT2A*-rearranged Acute Myeloid Leukemia Is Strongly Associated with Inferior Post-Transplant Outcome

Sun Loo, MBBS[1,2], Nicola Potter, PhD[3], Adam Ivey, PhD[4,5], Jenny O'Nions, MBBCh, PhD MRCP, FRCPath[6], Roderick Moon[5], Chun Yew Fong, MBBS, FRACP, FRCPA, PhD[7], Natasha Anstee[8], Ing Soo Tiong, FRACP,FRCPA,MPhil[4,9], Chong Chyn Chua, MBBS,FRACP,FRCPA, PhD[4,2], Jad Othman, MBBS[3,10,11], Hannah Renshaw[6], Robert Baker[12], Nigel H. Russell, MD[10], Ashish Bajel, FRACP[1], Hsin-An Hou, MD PhD[13], Richard Dillon, PhD MRCP, FRCPath[10,3], Andrew H. Wei, MBBS,PhD[14,15]

[1] Department of Haematology, Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Melbourne, Australia
[2] The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia
[3] Department of Medical and Molecular Genetics, King's College London, London, United Kingdom
[4] The Alfred Hospital and Monash University, Melbourne, Australia
[5] Human Molecular Pathology, The Alfred Hospital, Melbourne, Australia
[6] Department of Hematology, University College London NHS Foundation Trust, London, United Kingdom
[7] Austin Hospital, Heidelberg, Australia
[8] The Walter and Eliza Hall Institute of Medical Research, Parkville, AUS
[9] Peter MacCallum Cancer Centre, Melbourne, Australia
[10] Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[11] Royal North Shore Hospital, London, United Kingdom
[12] Health Service Laboratories, UCLH, London, United Kingdom
[13] Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[14] Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia
[15] The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Introduction

KMT2A-rearranged (*KMT2Ar*) acute myeloid leukemia (AML) is associated with inferior survival and allogeneic hematopoietic cell transplant (HCT) in first remission (CR1) is an important post-remission objective (Issa et al, Blood Cancer Journal 2021). Despite HCT, however, the relapse risk is ~50% (Menghrajani et al, Blood Adv. 2022). Several small cohort studies have described the prognostic utility of pre-HCT MRD assessment using real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR), but currently, this is not standard practice (Scholl et al, Haematologica 2005; Huang et al, Med Sci Monitor 2016; Liu et al, Biol Blood Marrow Transplant 2014; Heuser et al, Blood 2021). A significant barrier to widespread implementation of *KMT2A::X* MRD monitoring is the presence of diverse fusion-partner genes and varied breakpoint regions. The potential to detect and pre-emptively target pre-HCT *KMT2A::X* MRD has relevance with the development of menin inhibitors, which have been shown to be active in the clinic (Issa et al, Nature 2023). In the current work, we report the prognostic impact of pre-HCT *KMT2A::X* MRD detection by RT-qPCR and the relationship with post-HCT outcome in adults with *KMT2Ar* AML. We also describe a novel 3 common primer/probe *KMT2A::X* reverse transcription digital PCR (RT-dPCR) MRD assay as a simplified dPCR alternative to MRD monitoring.

Methods

Archived pre-HCT cDNA were available from 54 patients treated in the UK (including UK NCRI AML17 and AML19) and Australia. Samples were analyzed by RT-qPCR using previously described methods in 45 patients (Abildgaard et al, Eur J Haematol. 2013), and RT-dPCR in 9 patients (Ivey, unpublished 2023). The RT-dPCR method, which uses a common 3 primer/probe set to capture breakpoints within *KMT2A* obviating the need for fusion-gene specific plasmid standards, showed high concordance with RT-qPCR across 20 samples (R^2=0.9915) . Copy numbers were expressed per 100 ABL copies. Assay sensitivity was ~0.001%. Survival outcomes were estimated using the Kaplan-Meier method for relapse-free survival (RFS, date of HCT to relapse or death from any cause) and overall survival (OS, date of HCT to death or last follow-up). Cox proportional hazards

was used to assess variables impacting RFS and OS. Categorical variables were calculated using Fisher exact test and continuous variables using Mann-Whitney-U test. The study was approved by human research ethics committees (AUS 21/26; UK 14/WA/1056, NC10.13).

Results

A total of 54 patients with *KMT2A*r AML underwent HCT between 2010-2022. Median age was 43 years (range, 17-70), 63% were female, 94% had *de novo* AML, all had received prior intensive chemotherapy and 76% were transplanted in CR1, 50% with myeloablative conditioning. *KMT2A::X* subtypes included t(9;11)/ *KMT2A::MLLT3* in 35%, t(6;11)/ *KMT2A::AFDN* in 26%, t(11;19)/ *KMT2A::ELL* in 13% and *KMT2A::MLLT1* in 5%, t(10;11)/ *KMT2A::MLLT10* in 17% and other rare *KMT2A::X* variants in 4%. Pre-HCT MRD was detected (MRD-pos) in 46% of patients (25 of 54) at a median level of 0.3 copies/100ABL (range, 0.006-35.0394). The frequency of post-HCT relapse was significantly higher in patients with RT-qPCR/RT-dPCR levels $\geq$0.01% pre-HCT (68% relapsed vs 24% if MRD-neg, p=0.002) (Figure 1). Median time to relapse was 4.7 months (range, 0.8-22.5), with 100% of patients (22 of 22 with available molecular status at relapse) retaining the *KMT2A::X* variant at relapse. With median follow-up time of 37 months, pre-HCT *KMT2A::X* MRD-pos was associated with significantly inferior 2-year RFS (19% vs. 63%, p=0.0013) (Figure 2) and 2-year OS (47% vs. 69%, p=0.031). On univariate analysis, variables associated with inferior RFS were pre-HCT MRD-pos status (hazard ratio (HR) 3.2 [95% confidence interval (CI) 1.5-6.9], p=0.002) and transplant in second remission vs. CR1 (HR 2.6 [95% CI 1.2-5.5], p=0.01), however, pre-HCT MRD-pos status was the only variable associated with inferior RFS on multivariate analysis (HR 2.8 [95% CI 1.3-6.1], p=0.01).

Conclusions

Pre-HCT *KMT2A::X* MRD detection by RT-qPCR and RT-dPCR is a robust prognostic indicator of post-transplant relapse and inferior survival outcome. Targeting patients with *KMT2A::X* MRD positive disease pre-HCT using novel menin inhibitors is currently the subject of an enrolling clinical trial (AMLM26 INTERCEPT) (ACTRN12621000439842).

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Figure 1. Pre-transplant detection of *KMT2A::X* MRD is significantly associated with higher relapse risk

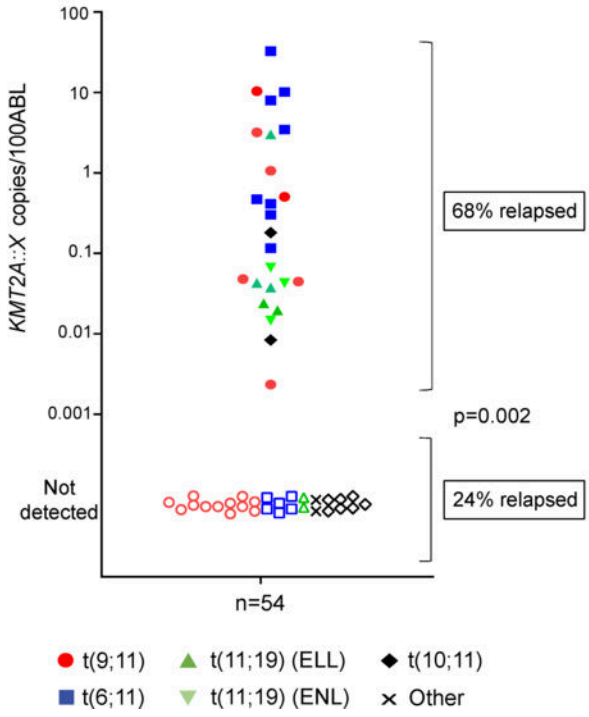

Figure 2. Relapse-free survival is significantly inferior in patients with pre-transplant *KMT2A::X* MRD detected vs. undetected

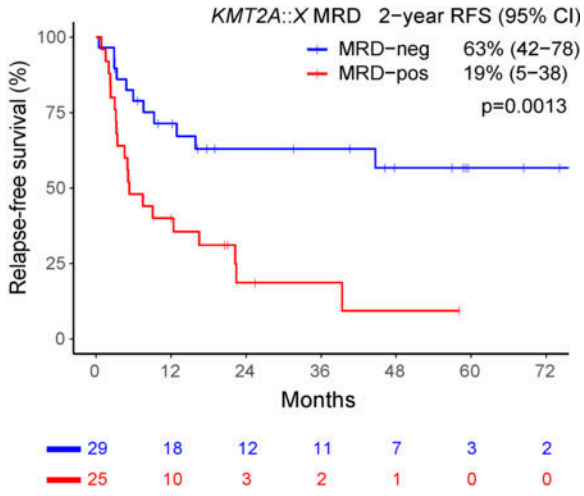

Figure 1

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