ELSEVIER

Blood 142 (2023) 4621–4622

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

High Prevalence of *IDH* Mutation in Myeloid Neoplasm with Concomitant Autoimmune Rheumatic Disorders

Lih En Hong, MBBS, FRACP[1], *Chung Hoow Kok, PhDBSc*[2,3], *Monika Kutyna, PhD*[4,3], *Joule J Li, MBBS, FRACP*[5], *Rakchha Chhetri, MBBS MHID Grad Cert. Biostat*[4], *David M. Ross, MBBS, PhD FRACP, FRCPA*[6,4], *Susan Branford, PhD*[7,8], *Hamish S Scott, PhDBSc*[7,8], *Anna Brown, PhDBSc*[8,7], *Christopher Norman Hahn, PhD*[7,8], *David T Yeung, MBBS,PhDBSc,FRACP,FRCPA*[3,4,2], *Mrinal M. Patnaik, MD MBBS*[9], *Mithun V Shah, MDPhD*[9], *Susanna Proudman*[1], *Mihir Wechalekar*[10], *Devendra Hiwase, MDMBBS,PhDFRACP,FRCPA*[3,4,2]

[1] Rheumatology Department, Royal Adelaide Hospital, Adelaide, Australia
[2] Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia
[3] Blood Cancer, Precision Medicine Theme, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia
[4] Haematology, Central Adelaide Local Health Network (CALHN), Adelaide, Australia
[5] Haematology, Royal Adelaide Hospital, Adelaide, Australia
[6] Department of Haematology, Flinders Medical Centre and University, Adelaide, Australia
[7] Genetics and Molecular Pathology, SA Pathology, Adelaide, Australia
[8] Centre for Cancer Biology, SA Pathology and University of South Australia, Adelaide, Australia
[9] Division of Hematology, Mayo Clinic, Rochester, MN
[10] Flinders University, Bedford Park, AUS

BACKGROUND: The association between myeloid neoplasm (MN) and autoimmune rheumatological diseases (AIRD) is increasingly recognized. Furthermore, prolonged cytotoxic disease modifying anti-rheumatological drugs (DMARD) for AIRD may potentially induce therapy-related MN (t-MN), a lethal haematological malignancy with dismal outcomes. However, the genetic association and mechanism underpinning immune dysfunction in patients with between MN and AIRD is not fully elucidated.

METHODS: In this collaborative study across the two disciplines and continents (Australia and USA), we assessed the burden of well-defined AIRD in a large cohort of MN (n=1702) that included myelodysplastic syndrome (MDS; n=861), acute myeloid leukaemia (AML; n=640), myeloproliferative neoplasm (MPN; n=89) and MDS/MPN overlap (n=112). We characterized the cytogenetic and mutational landscape of MN with AIRD (MN-AIRD) and without AIRD. In order to assess the mechanistic link between AIRD and MN, we investigated the bone marrow microenvironment in MN-AIRD *vs.* well-curated age matched controls.

RESULTS: 132 (7.75%) of MN (n=1702) had concomitant AIRD. Although association of AIRD was observed across all subtypes of MN, enrichment of AIRD was observed in patients with MDS, MDS/MPN and MPN compared to AML (9.5% vs. 9.8% vs 10.1% vs. 4.67%; P <0.001). Inflammatory arthritis (n=65; 49.24%) followed by inflammatory connective tissue diseases (CTD, n=23; 17.42%), polymyalgia rheumatica (PMR, n=18; 13.63%) and vasculitis (n=16; 12.12%) were the most prevalent AIRD in the MN cohort. Notably, 87.7% of inflammatory arthritis were rheumatoid arthritis (RA; n=57).

Striking survival differences were observed between t-MN without AIRD and MN-AIRD (14.0 *vs.* 33.7 months; P <0.0001) and t-MDS no-AIRD and MDS-AIRD (16.1 *vs.* 33.4 months, P =0.001). Chromosomal abnormalities including complex karyotype, monosomal karyotype, del 5q, del 7q, marker chromosome and *TP53* mutations were enriched in t-MN following independent primary cancer (t-MN without AIRD). However striking enrichment of *IDH*1 and *IDH2* (henceforth referred as *IDH*) mutations in MN with AIRD compared to MN without AIRD (20% *vs.* 11%, P =0.02), particularly in MDS-AIRD compared to MDS without AIRD (21% *vs.* 7%; P =0.001). The enrichment of IDH mutations were particularly prevalent in in MN cases with RA compared to other AIRD (34% *vs.* 11%; P =0.005). While *IDH* mutations were observed in only 8% and 6% of PMR and inflammatory CTD patients, respectively. Surprisingly higher frequency of *IDH* mutations was observed in evaluable seronegative compared to seropositive RA patients (62% vs. 0%; P =0.006). We also observed that majority of *IDH* mutations in seronegative RA were *IDH1* (6/8; 75%) while *IDH2* mutations were common other AIRD (6/6; 100%) (P =0.009).

We also assessed the impact of DMARDs on genomics of myeloid neoplasm. The majority of MN-AIRD patients treated with methotrexate did not harbor poor risk cytogenetic and mutation features such as complex karyotype, monosomal karyotype, del 5q, del 7q and/or *TP53* mutation. In contrast, the majority of patients who had cyclophosphamide harbored high risk cytogenetic and molecular features.

To assess pathogenic mechanisms linking MN and AIRD, we evaluated bone marrow microenvironment in myeloid neoplasm patients with and without AIRD. Bone marrow mesenchymal stromal cells (MSC) isolated from MN-AIRD were highly senescent compared to age matched healthy controls, MN without AIRD, with defective proliferating and differentiation capacity of MN-AIRD and secretion of highly proinflammatory cytokines and chemokines.

CONCLUSIONS: In summary, our key findings include: 7.8% of MN were associated with AIRD with stronger association of AIRD with MDS and MDS/MPN compared to AML and striking enrichment of *IDH* mutations in MN with inflammatory arthritis compared to MN with other AIRD (29% vs 11%; P =0.02), especially in seronegative RA compared to seropositive RA (62% vs. 0%; P =0.006). In contrast to cyclophosphamide and azathioprine, majority of cases treated with methotrexate **did not** harbor poor risk cytogenetic and/or *TP53* mutation. As methotrexate is widely used as an anchor drug in many rheumatology treatment regimens, this is a highly significant finding of clinical relevance.

Disclosures Ross: *Celgene/BMS:* Honoraria, Research Funding; *Menarini:* Membership on an entity's Board of Directors or advisory committees; *Keros:* Consultancy; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding; *Takeda:* Membership on an entity's Board of Directors or advisory committees. **Branford:** *Enliven:* Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Cepheid:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Qiagen:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Yeung:** *Takeda:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Patnaik:** *CTI Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Kura Oncology:* Research Funding; *StemLine:* Research Funding. **Shah:** *AbbVie:* Research Funding; *Astellas:* Research Funding; *MRKR Therapeutics:* Research Funding; *Celgene:* Research Funding.

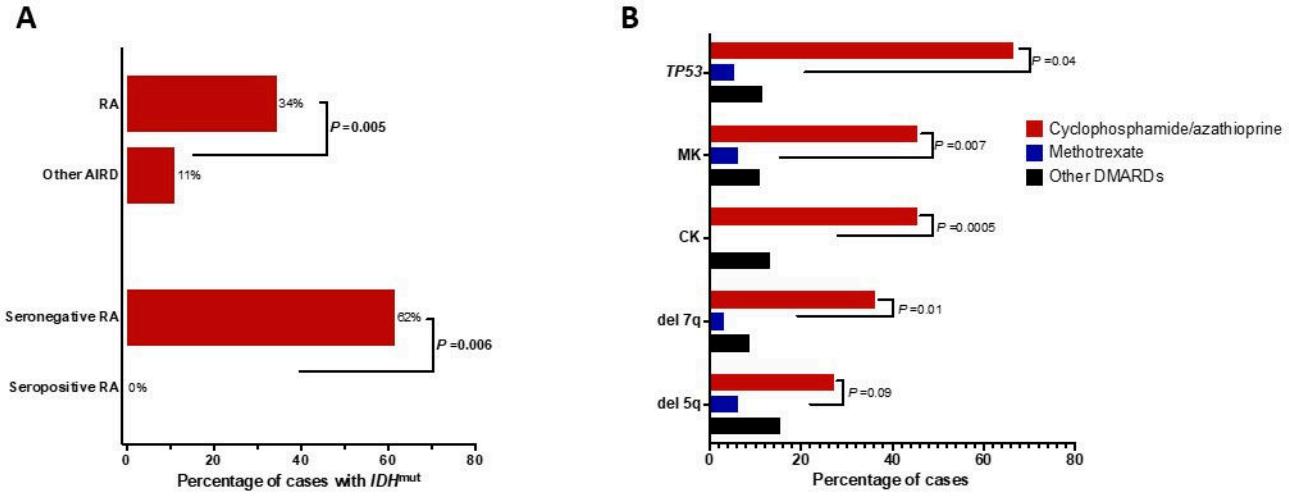

Figure 1: *IDH* mutations are highly enriched in myeloid neoplasm with seronegative Rheumatoid arthritis (RA). (A) *IDH* mutations are highly enriched in seronegative RA as compared to seropositive RA and other AIRD. (B) In contrast to cyclophosphamide and azathioprine, majority of cases treated with methotrexate **did not** harbor poor risk cytogenetic and/or *TP53* mutation.

Figure 1

https://doi.org/10.1182/blood-2023-190809