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Population-based screening for IgM MGUS in Iceland: The iStopMM experience

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Introduction:
Monoclonal gammopathy of undetermined significance (MGUS) with IgM paraproteins (IgM MGUS) is an asymptomatic precursor condition of Waldenström macroglobulinemia (WM) and related lymphoproliferative disorders, constituting 15-20% of MGUS cases. Because IgM MGUS is asymptomatic it usually goes undetected until progression into symptomatic disease. Therefore, the characteristics of the underlying IgM MGUS population are not well known and the clinical utility of detecting IgM MGUS is unclear. Here we describe the IgM MGUS specific results of the Iceland screens, treats, or prevents multiple myeloma (iStopMM) screening study and randomized trial of follow-up strategies.

Methods:
All residents of Iceland in September 2016 over the age of 40 were offered participation and 80,759 provided written informed consent and 75,422 were screened for MGUS by serum protein electrophoresis (SPEP) and free light-chain (FLC) assay and immunofixation to confirm the presence of paraproteins. Those with MGUS were randomized to three study arms, arm 1 which continues as if they were never screened, arms 2 and 3 were called into a clinical research center for follow-up including bone marrow sampling and computerized tomography (CT) of the abdomen and thorax and at least annual follow-up.

Results:
Of the 3,666 participants with MGUS, 906 (25%) had an IgM paraprotein, of whom 20% had multiple paraproteins on the same SPEP and immunofixation. The prevalence of IgM MGUS in the population >40 years was 1.2%. A total of 825 participants with new IgM MGUS were randomized and 534 participants randomized to arms 2 and 3 visited the study clinic. Baseline evaluations showed that 48 (9%) had ≥10% plasma cells/lymphoplasmacytic cells in the bone marrow and 29 (5%) had lymphadenopathy on CT. At the same first visit, 4 (0.7%), 2 (0.4%), and 1 (0.2%) were diagnosed with WM, CLL and NHL respectively. Over a median follow-up of 4.5 years those randomized to active follow-up (arms 2 and 3) had a significantly higher likelihood of a composite endpoint of smoldering WM (SWM) or active WM or related malignancy (p=0.001; Figure) compared to those with IgM MGUS randomized to arm 1 but not after excluding smoldering/asymptomatic disease (p=0.64; Figure). Those who were randomized to active follow and later diagnosed with WM or other

malignancy were diagnosed 1.7 years after screening compared to 3.1 years in those not in follow-up (p=0.07).

Discussion:

This is the largest screened cohort with IgM MGUS and first randomized trial of follow-up strategies. The prevalence of IgM paraproteins was slightly higher than reported previously representing a fourth of MGUS cases, partly by including those with multiple paraproteins which appear common in those with IgM MGUS. At baseline, 9% had ≥10% bone marrow plasma/lymphoplasmacytic and 5% had lymphadenopathy at baseline. Randomization to active follow-up led to more diagnoses of advanced precursors and possibly to earlier diagnosis of WM and related malignancies. Whether this translates into improved outcomes is not clear, but future studies in the cohort are likely to improve our understanding of IgM MGUS and its origins, patterns of progression, and management.

Figure: Cumulative hazard graphs of A: Smoldering WM or more advanced disease and B: only non-smoldering advanced disease, by randomization arms 1 (Control) and arm 2 and 3 (Intervention).