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Determination of MYD88 and CXCR4 mutation for clinical detection and their significance in Waldenström macroglobulinemia

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Introduction

Waldenström macroglobulinemia (WM) is a rare B-cell lymphoma characterized by prevalent MYD88 and CXCR4 mutations. Despite their importance, standardized approaches for detecting these mutations are limited. Additionally, few studies have integrated these gene mutations with routine clinical features for prognostic analysis across various therapeutic backgrounds.

Methods

In this study, 385 symptomatic WM patients were analyzed for MYD88 and CXCR4 mutations using Sanger sequencing, next-generation sequencing (NGS), allele-specific quantitative polymerase chain reaction (AS-PCR), and/or droplet digital PCR (ddPCR).

Results

A total of 385 patients were assessed for the MYD88 mutation. Among them, 233 were tested by Sanger sequencing, 246 by NGS, 322 by AS-PCR, and 214 by ddPCR. The overall MYD88 mutation rate was 87.8%. AS-PCR and ddPCR demonstrated the highest sensitivity (98.5% and 97.7%, respectively). Specifically, a high false-negative rate for MYD88 was observed with Sanger sequencing and NGS in patients with tumor burdens less than 10% (40.8% and 23.0%, respectively). There was no significant difference in the MYD88 mutation rate detected by ddPCR and AS-PCR among patients with varying tumor burdens (P=0.149 and P=0.346, respectively). MYD88 mutations were detected at high incidences of 80.0% and 79.2% in specimens with less than 10% infiltrated tumor cells using ddPCR and AS-PCR, respectively.

CXCR4 mutation testing was performed on 362 patients, with 273 tested by Sanger sequencing, 246 by NGS, and 318 by AS-PCR. Overall, 30.9% of patients had the

CXCR4 mutation. NGS exhibited the highest sensitivity (78.0%) among the three detection methods.

Among the 385 WM patients, 47 (12.2%) were classified as MYD88 wild-type. These patients exhibited a significantly lower proportion of males and lymphadenopathy, but a higher proportion of hepatomegaly and splenomegaly. Additionally, MYD88 wild-type patients showed a notably higher proportion of elevated LDH. However, there were no significant differences in progression-free survival (PFS) or overall survival (OS) between MYD88 wild-type and MYD88 mutation groups (P=0.112 and P=0.451, respectively). Thewild-type group exhibited inferior PFS compared to the mutated group under BTKi-based therapy (P=0.014).

Patients with CXCR4 mutations had a significantly higher proportion of individuals older than 65 years, and higher rates of anemia and thrombocytopenia. The CXCR4-mutated group also had a significantly higher proportion of patients with serum IgM levels exceeding 40g/L and serum β2-MG levels above 3 mg/L. Notably, the CXCR4 mutation group had significantly worse survival compared to the wild-type group (P=0.024 for PFS and P=0.022 for OS). Patients with CXCR4 mutations experienced inferior PFS (P=0.04) and OS (P=0.03) in BTKi therapy groups.

Multivariate analysis indicated that MYD88 and CXCR4 mutations were not independent prognostic factors in the non-BTKi group when considering IPSSWM clinical staging. However, in the BTKi treatment group, these mutations emerged as independent adverse prognostic factors, overshadowing the prognostic significance of IPSSWM classification (MYD88: HR=0.229, P=0.030; CXCR4: HR=3.349, P=0.012).

Conclusions

AS-PCR and ddPCR proved highly sensitive for MYD88 mutation detection, particularly in low-infiltrated WM. NGS was the most sensitive method for detecting CXCR4 mutations. Under BTKi treatment, MYD88 and CXCR4 mutations were shown to have greater prognostic significance than IPSSWM staging in WM.