

Second primary malignancies after bendamustine-rituximab in indolent lymphomas: increased risk in Waldenström Macroglobulinemia? A comparative analysis with follicular lymphoma from FIL FOLL12 trial.

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The prolonged survival of patients with Waldenström Macroglobulinemia (WM) has raised concerns about long-term complications, including second primary malignancies (SPMs), and real-world data remain limited. We aimed to evaluate, in a multicenter real-life cohort, the incidence, type, and risk factors of SPMs in WM patients treated with bendamustine-rituximab (BR), and to compare them with follicular lymphoma (FL), treated with BR in the FIL FOLL12 trial. FL represents an ideal comparator, as both diseases are commonly treated with frontline BR but differ substantially in their underlying biology and natural history.

We retrospectively analyzed 168 WM patients (median follow-up 6.8 years) and 341 FL patients (median follow-up 8.4 years). Median age at diagnosis was 65 years (IQR 57–74) in WM and 64 (IQR 55–71) in FL; M/F ratio was 2.2 vs 0.7, respectively.

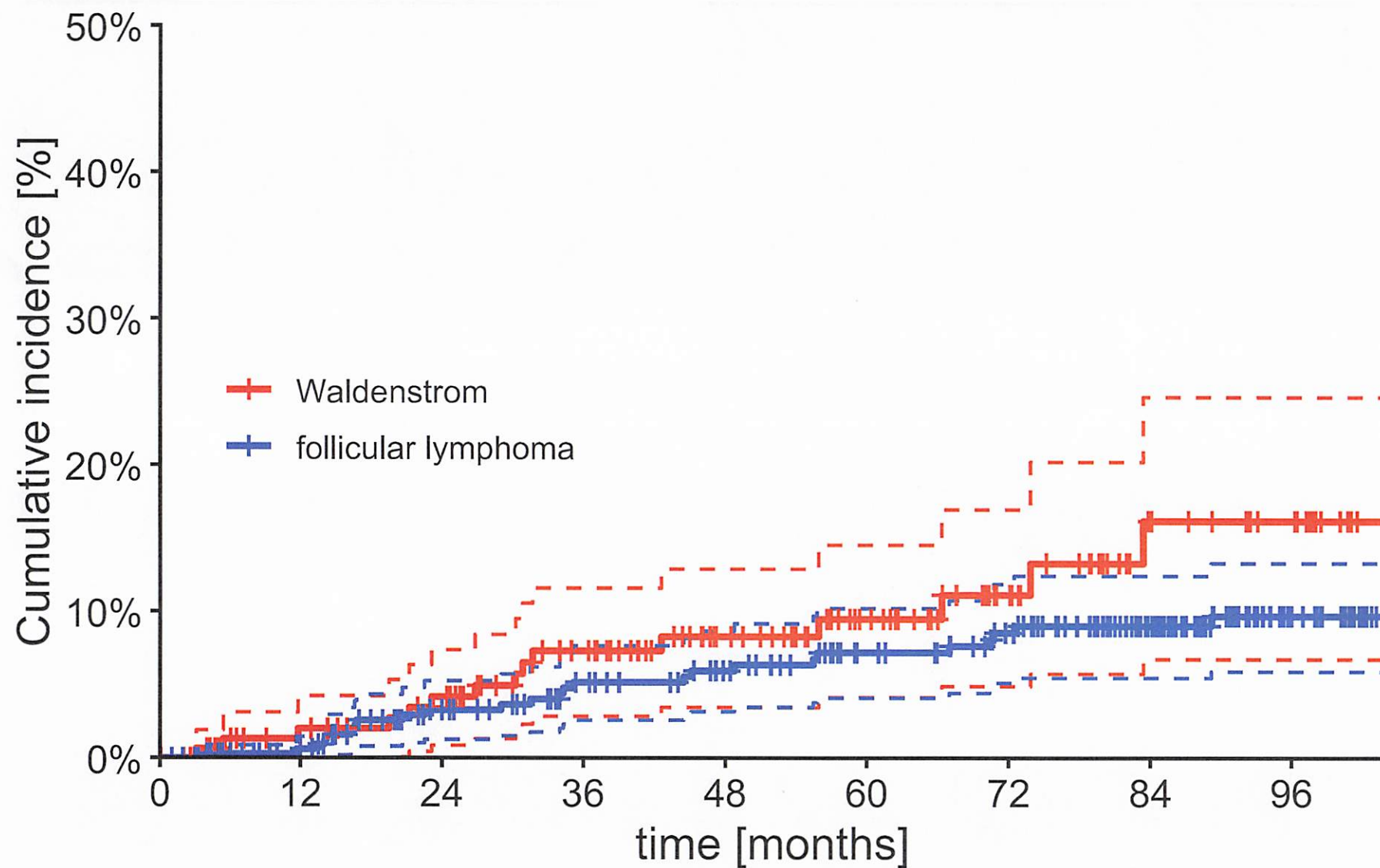
In WM, median overall survival (OS) was not reached, while median progression-free survival (PFS) was 8.9 years and event-free survival (EFS, time to relapse, death from any cause, or SPM) was 6.8 years. Fifty patients (29.8%) relapsed, and 44 (26.2%) received second-line therapy. Considering only the time between first line with BR until starting of second line or at last follow-up for patients who did not receive a second line treatment, SPMs occurred in 15 WM patients (9.1%; male 10.6%, 12 out of 113 vs female 5.8%, 3 out of 52): 12 solid (4 prostate and 2 colorectal carcinomas, 1 melanoma, 1 hepatocarcinoma, 1 esophagus carcinoma, 1 urothelial and 1 neuroendocrine

neoplasm, 1 seminoma) and 3 hematologic (2 myelodysplastic syndromes, 1 acute myeloid leukemia).

In FL, OS, PFS, and EFS were not reached; 105 patients (30.8%) relapsed and 75 (22%) received second-line therapy. In the same condition, SPMs occurred in 27 patients (7.9%, male 8.6%, 12 out of 139 vs female 7.4%, 15 out of 202): 25 solid tumors (7 breast, 5 colorectal, 3 lung, 2 gastric, 1 bladder, 1 parotid, 1 thyroid, 1 melanoma, 1 myosarcoma, 1 neuroendocrine, and 2 unknown primary site) and 2 hematologic (2 myelodysplastic syndromes).

Cumulative SPM incidence in WM was 8.3% and 16.2% at 48- and 96-month, respectively, vs 5.9% and 9.7% in FL (Figure 1). The incidence observed in WM is consistent with previous reports (Leblond et al., Leukemia 2026 in which SPM cumulative incidence was 17.6% at 96 months, $p=0.79$). WM patients showed a higher incidence of SPMs at 96 months compared to FL ($p=0.03$). Deaths related to SPMs were proportionally more frequent in WM (8/31, 25.8%) than in FL (10/64, 15.6%).

In conclusion, WM patients treated with BR showed a higher incidence of SPMs than FL patients treated with the same regimen, suggesting that disease-specific factors, in addition to treatment exposure, may contribute to the increased oncologic risk. These findings support structured long-term surveillance and prevention of tumor risk factors in WM and prospective studies to clarify the drivers of increased oncologic risk, including treatment, disease biology, and patient susceptibility.



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