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Incidence, Risk Factors and Outcomes of Second Primary Malignancies in Waldenström's Macroglobulinaemia

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A similar abstract was presented in European Haematology Association 2024 in Madrid. This abstract contains updated cohort with further in-depth analysis.

Background

It has been suggested that the incidence of second primary malignancies (SPMs) in patients with Waldenstrom's Macroglobulinaemia (WM) is higher than in the general population potentially due to immune dysregulation, older age and exposure to cytotoxic therapy. The incidence of malignancies has not been previously reported in the United Kingdom (UK). We aimed to assess the incidence of co-existing malignancies and determine risk factors and outcomes of patients with second primary malignancy in a UK referral centre.

Methods

We undertook a retrospective review of all patients with a diagnosis of WM at a University College London Hospital (UCLH) between 1984-2024. Electronic healthcare records system was used to identify the patients diagnosed with another malignancy.

Results

A total of 566 patients with WM were identified, with median follow up of 87 months (range 0-479). Co-existing malignancies were recorded in 136 (24%) patients, and a total number of 171 separate cancer diagnoses made (including those with pre-existing malignancies prior to WM diagnosis). SPM was established in 103/136 (75.7%) cases after WM diagnosis, with a median time from WM diagnosis to SPM of 74 months (range 8-288). The incidence rate of SPM was 2.9% per person year. Second haematological malignancy was most common (n=41), followed by skin (n=31) neoplasms (fig. 1).

A total of 439/566 (77.6%) patients had received treatment for WM with median 2 lines of therapy per patient. The SPM occurred after frontline therapy in 79/136 (58.1%). Of patients (n=159) treated with Bruton's Tyrosine Kinase inhibitors (BTKIs), 23 (12%) developed SPM on therapy or thereafter. Of these, 5/23 (22%) patients developed DLBCL. Haematological and skin cancers were also the most common (fig. 2). Median duration of drug exposure was 25 (0-96) months prior to development of SPM.

On univariable analysis, female sex (p=0.015) and increasing age (p=<0.001) were risk factors for SPM, but significance was not reached by multivariable analysis (fig. 3). Exposure to chemotherapy was not associated with a significantly higher rate of SPM (p=0.51), and no specific regimen was significantly associated with higher incidence, including bendamustine (p 0.418).

Median overall survival (OS) was not reached in either cohort (fig. 4). The OS at 5-years for WM patients without SPM was 88%, and 85% for patients with SPM (p=0.15).

High grade transformation (HGT) occurred in 17/566 (3%) patients, at a rate of 0.4% per patient year. Median OS following HGT was 39 months (95% CI 10-NR), with estimated 3-year OS 66.6%

(95% CI:38.6-91.0%) and 5-year OS 39.5% (19.4-80.3%). Secondary myelodysplastic syndrome was recorded in 1/566 patients.

Conclusion

A quarter of WM patients had a diagnosis of another malignancy. The predominant SPMs were haematological followed by skin neoplasms and the incidence of SPMs in patients with BTKIs was 12%. Exposure to chemotherapy was not associated with a significantly higher rate of SPMs. Survival rates were not significantly different in patients with SPMs. With the limitations of a retrospective study and small numbers, these findings highlight the importance of clinical surveillance for symptoms and signs of SPMs in patients with WM/LPL.

500 words

Figure 1. Table demonstrating patient cohort characteristics, details of their treatment and co-existing malignancy.

Patient characteristics	n=566
Age, median (range)	62 (30-89) years
Male	320 (56.5%)
Female	246 (43.6%)
Patient Characteristics	n=566
Type of treatment given	n=986
BTKI	159
BR	136
DRC	135
Rituximab monotherapy	94
R-CHOP	60
Bortezomib combination	46
ASCT	42
Chlorambucil	39
Fludarabine	36
RCVP	35
Other	116
Total	986
Type of co-existing malignancy	n=171
Haematological	41 (24.0%)
Dermatological	31 (18.1%)
Prostate	28 (16.4%)
Breast	22 (12.8%)
Pulmonary	13 (7.6%)
Colorectal	10 (5.8%)
Vesicular	10 (5.8%)
Other	16 (9.4%)
Total	171

Figure 2. Table showing type of SPM developed during BTK-inhibitor therapy

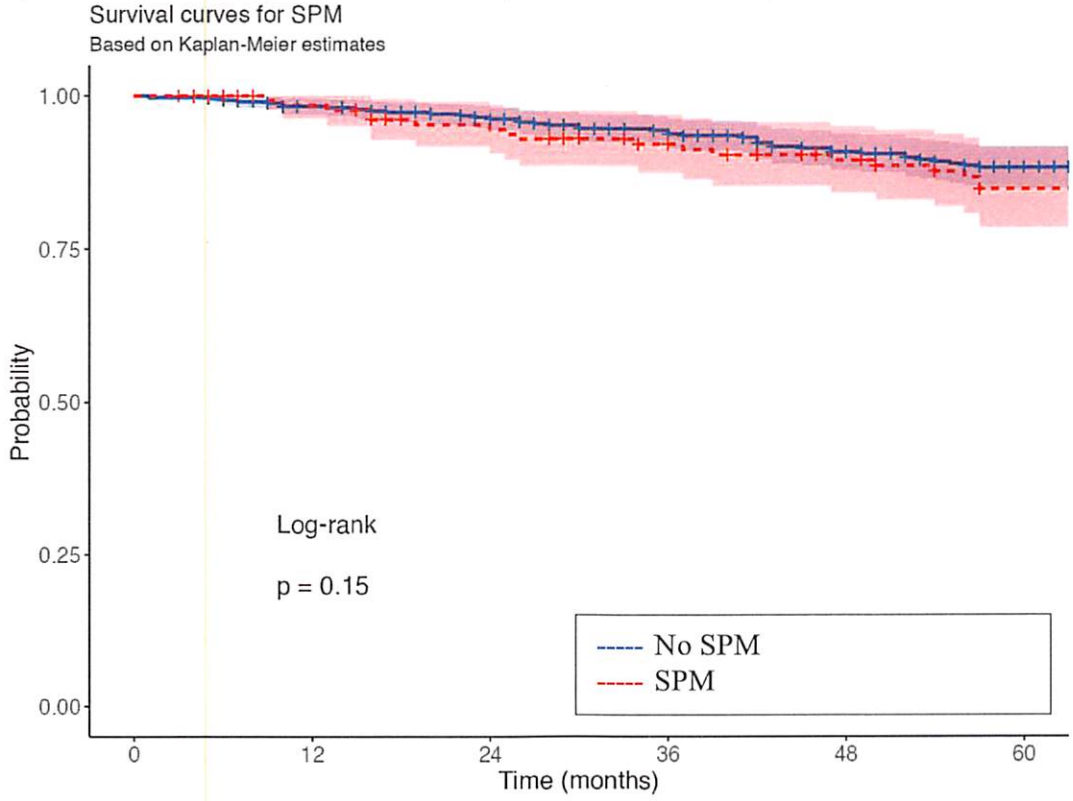
Type of SPM	Number and proportion of cases
Haematological	7 (30.4%)

Dermatological	7 (30.4%)
Prostate	3 (13.0%)
Pulmonary	3 (13.0%)
Colorectal	1 (4.3%)
Vesicular	1 (4.3%)
Other	1 (4.3%)
Total	23

Figure 3. Univariable and multivariable analysis of possible risk factors for the development of SPM in patients with WM

	Univariable analysis		*Multivariable analysis*	
Variable	Hazard ratio	P-value		
Male sex	0.41-0.91	0.015*	0.19-16.9	0.614
IPSS	0.99-1.55	0.066		
MYD88^{L265P}	0.65-4.09	0.299		
CXCR4^{MUT}	0.02-0.19	0.072		
Exposure to chemotherapy		0.513		
Lines of therapy	0.97-1.09	0.408		
Age	1.02-1.04	<0.001*	0.94-1.16	0.443
Bendamustine	0.49-1.34	0.418		

Figure 4. Comparison of 5-year overall survival for patients with no SPM compared to patients with SPM



					95% Confidence Interval	
Levels	**time**	**Number at Risk**	**Number of Events**	**Survival**	**Lower**	**Upper**
NO SPM	60	261	18	88.1 %	84.8 %	91.6 %
SPM	60	88	8	84.7 %	78.4 %	91.5 %