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Second primary malignancies and disease transformation in symptomatic patients with Waldenstrom's Macroglobulinemia: Outcomes of a population-based analysis

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Background

Waldenström's Macroglobulinemia (WM) is associated with heterogeneous clinical presentation and prolonged survival, during which a second primary malignancy (SPM) or transformation to high grade lymphoma may occur post treatment initiation. Although several studies have been published, further data after prolonged follow up are required, due to possible late onset of such complications.

Methods

Symptomatic patients with WM were prospectively enrolled. The incidence of a second malignancy, paying attention to the type of second tumor and the date of diagnosis, as well as the disease transformation were recorded.

Results

711 symptomatic newly diagnosed patients were enrolled [median follow up: 186 months, median age: 69 years, females: 40.8%, 339 (47.7%) have died]. Primary treatment was anti-CD20 monoclonal antibodies-based (rituximab) combinations in 59.5%, contained alkylating agents (bendamustine, cyclophosphamide) in 68.2%, a nucleoside analogue (fludarabine, cladribine) in 2%, proteasome inhibitors in 8.8% and Bruton's tyrosine kinase (BTK) inhibitors in 8.1%.

61 patients (8.6%) were diagnosed with an SPM [lung (18.0%), hematological malignancies (14.8%), colorectal (11.5%), gastrointestinal (11.5%), prostate (9.8%), non-melanotic skin tumors (8.2%), breast (4.9%), urothelial (4.9%), head and neck (3.2%), central nervous system (1.6%), ovarian (1.6%), thyroid (1.6%), renal (1.6%), pancreas (1.6%), glioma (1.6%) and other (3.2%). The median time from treatment initiation to the diagnosis of an SPM was 57 months. The incidence rate (IR) of an SPM was 0.009 per person-years. The IR of an SPM was higher in men ($p=0.042$), but no difference was recorded concerning the age or the agent used, while the risk of death from WM or other causes was 28.3% and 17.9%, respectively.

Moreover, in 12 patients (1.7%), the diagnosis of symptomatic WM followed the diagnosis of another malignancy and the overall survival analysis showed an association of the existing malignancy with a twofold increase in the risk of death, though results were marginally not significant [HR = 2.01, CI (0.99, 4.06), $p = 0.051$].

As far as the transformation to high grade lymphoma is concerned, 27 (3.8%) events were identified. The median time from treatment initiation to transformation was 70 months. The IR for transformation was 0.004 per person-years, while the cumulative incidence for transformation, accounting for death of any cause as a competing event, was 3% at 15 years. No increased risk of transformation was found in patients that received alkylating agents as a primary treatment. Although the number of patients that received therapy with nucleoside

analogues, proteasome inhibitors and BTK inhibitors was small, we identified no increased risk.

Conclusions

The incidence of a SPM in symptomatic patients with WM post treatment initiation was 8.6%, whereas transformation to high grade lymphoma was 3.8%. No significant correlation was found with the use of alkylators or other specific agents. This data emphasizes the need for screening for the most common malignancies among patients with WM, due to the prolonged survival of the disease.