Incidence and clinical correlates of non-immune cytopenia at diagnosis of chronic lymphocytic leukemia

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Introduction

Cytopenias due to bone marrow infiltration define Rai stages III-IV and Binet C in chronic lymphocytic leukemia (CLL) and are usually associated with poor outcome and, consequently, need for therapy. We aimed at ascertaining the incidence of cytopenia in a large series of unselected patients with CLL, its origin, clinical correlates and outcome.

Methods

In our single-center database of 781 patients with CLL diagnosed between 1979 and 2022, we identified those who presented with anemia (Hb < 11 g/dL) and/or thrombocytopenia (platelets under 100 x10^9/L) at diagnosis. The main aims were to describe their prevalence, clinical and biological characteristics, as well as their impact on progression-free survival (PFS) and overall survival (OS).

Results

Patient characteristics and incidence

Among 781 patients with CLL we identified 81 with anemia and/or thrombocytopenia at diagnosis (10.3%): forty-three (5.5%) had only anemia, 22 (2.8%) only thrombocytopenia, and 16 (2%) both anemia and thrombocytopenia. All cases were due to bone marrow infiltration but seven: five had autoimmune hemolytic anemia (AIHA) and two immune thrombocytopenia (ITP). These latter cases were not included in the survival analysis. The median follow-up was 53 months (range, 0-275).

The median age of the patients was 73 years. Patients who presented both anemia and thrombocytopenia were younger than those with either anemia or thrombocytopenia (median age 58 vs 75 years, p=0.04), had a higher incidence of lymphadenopathy (91% vs 36%, p<0.01), presented B symptoms more frequently (50% vs 9%, p<0.001), and had a higher median lymphocyte count (75.000 vs 7.925 x106/L, p<0.01), see Fig. 1A-B.

Prognosis

The 74 patients with non-immune cytopenia at diagnosis were analyzed for survival data. Patients with both anemia and thrombocytopenia presented a shorter time to first treatment -- TTFT- [median 0 months (95% CI 0-2 months)] when compared to patients with only anemia [median 3 months (95% CI 0-10 months)] or thrombocytopenia [median 10 (95% CI 0-30 months)], p<0.001. However, no differences were observed in PFS or OS.

Overall, 49 of 74 patients received upfront treatment. The patients in which cytopenia was the only treatment criterion (n=17) presented a longer PFS and OS compared to those with more than one criterion to start therapy (n=32): median PFS, 64 vs 60 months (p=0.06); median OS, 188 vs 73 months, p=0.04 (Fig. 1C-D).

After initial treatment, 13 patients dropped from Rai III-IV to Rai 0, and 36 from Rai III-IV to Rai I-II. In an exploratory analysis, we compared the survival of the patients who shifted to Rai 0 to another cohort of patients with CLL from our database who presented Rai 0 stage at diagnosis and required treatment (n=170). The analysis showed a shorter PFS (median 54 vs 184 months, p<0.001) and OS (median 65 vs 192 months, p<0.001) for the patients who had cytopenia at diagnosis that was resolved after therapy (downstaged to Rai 0) versus those who had Rai 0 at diagnosis (Fig. 2A-B).

Similarly, patients who dropped to Rai I-II were compared with patients Rai I-II at diagnosis (n=45). Patients downstaged to Rai I-II presented a shorter PFS (median 66 vs 103 months, p=0.02) with no differences in OS (Fig. 2C-D).

Conclusions

In our single-center series of 781 patients with CLL, around 10% presented with any non-immune cytopenia at the time of diagnosis (53% only had anemia, 28% only thrombocytopenia, and 19% both). While some patients with isolated non-immune thrombocytopenia could be closely followed without requiring upfront treatment (most likely because of the variety of mechanisms accounting for thrombocytopenia), those who have anemia or both cytopenia at diagnosis usually require immediate treatment (median TTFT 0 months). However, no differences were observed in PFS or OS. Importantly, patients with CLL with cytopenia at diagnosis had an adverse prognosis even if the cytopenia resolved upon initial therapy, a concept that warrants further consideration because of its implication when planning the treatment strategy.

Figure 1. Proportion of lymphadenopathy and B symptoms (A), absolute lymphocyte count (B), PFS and OS by treatment reason (C and D)

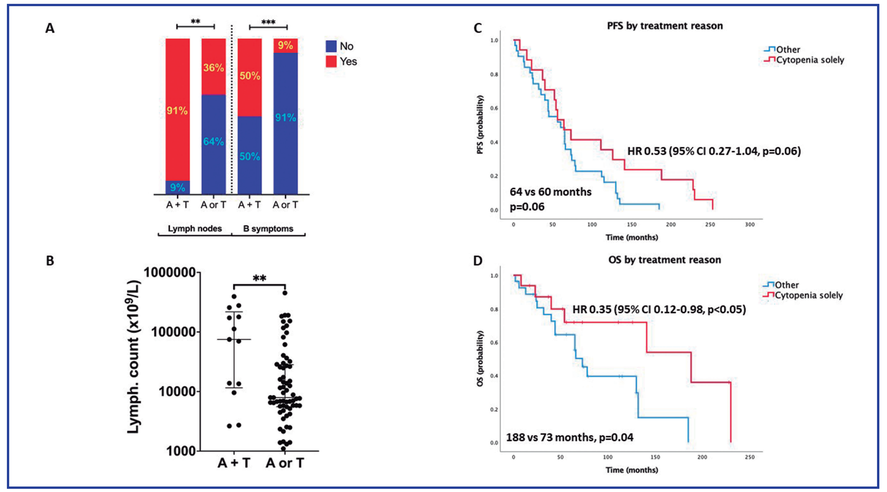

Figure 2. PFS and OS by cytopenia at diagnosis in Rai 0 (A and B) and in Rai I-II (C and D)