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641. CHRONIC LYMPHOCYTIC LEUKEMIA: BASIC AND TRANSLATIONAL

Immune reconstitution after venetoclax-based treatments in CLL

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Abstract Background: Chronic lymphocytic leukemia (CLL)-associated hypogammaglobulinemia is well-established. A degree of humoral immune reconstitution has been reported after ibrutinib and after venetoclax plus rituximab (Ven + R). We assessed improvement in immunoglobulin levels after different Ven-based treatments, including Ven monotherapy, combinations with rituximab or obinutuzumab (Ven + O), and combination with ibrutinib (Ven + I).

Methods: Patients with CLL who received treatment with Ven at our single center during the years 2012-2024 were evaluated in this retrospective chart review analysis. Recurrent courses of Ven were each considered discretely. Patients were excluded from analysis if they did not have at least 1 quantitative immunoglobulin measurement both within 1 year prior to Ven initiation and post-treatment. Patients with a paraprotein were excluded from analysis of that Ig class. Patients who received IVIG were excluded from IgG analysis. Data were extracted from time of Ven treatment start until subsequent treatment for CLL.

Results: 91 cases of Ven treatment were identified for chart review, including 86 unique patients and 5 instances of Ven re-treatment. 5 patients were excluded from IgM analysis due to IgM paraprotein. 51 patients were excluded from IgG analysis due to being on IVIG.

Patient population had a median age of 69 at Ven initiation. 79% (72 of 91 patients) had received prior CLL treatment, with a median number of 3 prior unique treatment regimens. Ven treatments were: Ven monotherapy- 35% (32 patients); Ven + R- 18% (16 patients); Ven + O- 31% (28 patients); and Ven + I- 16% (15 patients). Median time on Ven was 15.1 months. Overall, 74% (67 patients) achieved uMRD (< 0.01% CLL cells in peripheral blood). 50.5% (46 patients) had eventual CLL progression either on or after Ven treatment, with median 17.3 months from the end of Ven to next treatment (range 0 – 59.5 months).

For the overall population, median IgA levels decreased from pre-treatment to end of treatment (38 to 24.5 mg/dL, $p=0.01$; paired t-test). This was followed by a gradual increase starting 12 months after end of treatment, reaching statistical significance at month 36 (median IgA 52 mg/dL, $p = 0.02$). IgM levels trended similarly, with a significant increase from a median of 20 mg/dL at baseline to 37 mg/dL at month 36 ($p = 0.02$). IgG levels did not change significantly, though the exclusion of patients on IVIG limited this analysis.

The different treatment regimens had distinct effects on IgA levels. Patients treated with Ven + CD20 mAb had a significant reduction in the IgA at the end of treatment (baseline median 41 mg/dL to 20.5 mg/dL, $p=0.024$). Levels then rose gradually during treatment-free remissions, and were significantly higher than baseline by month 36 (median 53 mg/dL, $p=0.03$). The IgA trajectories were similar for patients treated with Ven + R or Ven + G.

In contrast, patients treated with Ven monotherapy did not have a statistically significant decrease of IgA levels (baseline median 34 mg/dL to 26.5 mg/dL, $p = 0.1$) and there was no increase from baseline after treatment.

Notably, patients treated with Ven + I did not have a statistically significant reduction after treatment, but did have a significant increase in IgA from baseline at later time points (baseline median 41 mg/dL to 84.5 mg/dL at month 48, $p = 0.05$).

We assessed for factors associated with superior IgA increase, defined as either a 50% improvement or improvement to the reference range (>80 mg/dL for our institution) at any time after Ven treatment. 21% (19 of 91 patients) had a superior IgA increase. Treatment regimen (Ven mono versus Ven + CD20 versus Ven + I) was also not associated with superior IgA increase. 84% of patients with superior IgA increase had a uMRD response to treatment (16 of 19 patients), compared to a 71% uMRD rate for patients who did not (51 of 72 patients), but this difference was also not statistically significant ($p= 0.3$, Chi-squared test).

Conclusions:

Our findings support that humoral immune reconstitution can be achieved after Ven-based treatment, based on recovery of IgA levels. IgA levels improved after Ven + CD20 therapy, as per prior reports, though Ven + CD20 mAb resulted in more significant initial reduction in IgA levels than Ven monotherapy or Ven + I. Interestingly, we did not find an association between superior IgA increases and depth of response.

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