COMMENTARY

Title: Immunomodulation mediated by polyclonal IgG replacement in patients with CLL may be important in infection prevention

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We read with interest the article by Idanna Innocenti and colleagues where a fixed dose of 10g hyaluronidase-free SCIg (subcutaneous immunoglobulin IgG) was administered every two weeks for one year to 10 patients with chronic lymphocytic leukaemia (CLL) and was highly effective in preventing infections [1]. It is generally accepted that frequency of infusions with hyaluronidase-free SCIg preparations are once weekly to maintain 'adequate' trough IgG [2], but this has been extrapolated from use in primary immunodeficient patients who typically have a complete antibody deficiency in contrast to the deficit observed in CLL

The findings from this small group of patients by Innocenti *et al* show that (i) dosing based on body weight or ideal body weight may not be necessary in secondary antibody deficiency conditions like CLL; (ii) reduced infusion frequency can be equally effective; (iii) immunomodulation mediated by polyclonal IgG replacement therapy (IgRT) also prevents infections. Just as high-dose immunoglobulin therapy is the current standard of care for immune-mediated thrombocytopenia, low-dose IgRT in CLL (especially with BTK inhibitor therapy, BTKi) over time may reverse the autoimmune cytopenias by modulating autoreactive B cell clones, which would then allow T-cell escape from the cytokine-mediated immunosuppressive environment [3]. This would lead to a decreased incidence of all types of infections (bacterial and non-bacterial) and improvement in the quality of life.

Our previously published retrospective analysis on 29 ibrutinib-treated CLL patients found that although long-term use of BTKi was not associated with serious infectious episodes, it neither reversed pre-existing hypogammaglobulinemia nor affected overall survival [4]. Three patients required IgRT given via SCIg (once weekly, treatment duration 3-11 years until 2020). None had further infection episodes and two patients had no recurrence of autoimmune haemolytic anemia on IgRT. One CLL patient (*ATM* 11q23del) who died had required five lines of therapy (including venetoclax), received IgRT for 6.5 years and ibrutinib for 16 months with one documented minor infection on ibrutinib therapy (death not related to disease progression or overwhelming sepsis). The two surviving patients had normal FISH at diagnosis.

Spaner et al showed that SCIg preparation has the ability to impair B-cell receptor (BCR) signalling, activation and TNFα secretion by CLL cells (in vitro stimulation). In addition, SCIg administration increased the trough IgG to >9g/L lowered TNFα and beta-2-microglobulin in blood suggesting IgRT may have anti-leukemic activity in CLL patients [5]. The authors discuss the possible mechanism is modulation via FcγRIIb, the IgG inhibitory receptor, that is predominantly on CLL cells; and low levels of this inhibitory receptor is independent of known prognostic markers but associated with a worse outcome [6].

Ana Colado and colleagues study into CLL T-lymphocyte responses to the administration of immunoglobulin preparations enriched with IgA and IgM (e.g.,

Pentaglobin™) demonstrated that this preparation had a lower inhibitory effect on T cell proliferation than standard IgG only preparations. This preparation decreased numbers of T cell apoptosis induced by venetoclax (in vitro cultures) but did not impair venetoclax-induced apoptosis of leukemic B cells [7]. Thus, this type of enriched Ig preparation may help restore T cell function earlier if used concurrently with BTKi therapies than currently achieved after several months of therapy [8].

In conclusion, the study by Idanna Innocenti and colleagues rightly calls into question the current criteria for selection of IgRT in CLL based on reliance upon infection frequency and serum IgG level. As IgRT has the ability to rescue T-cells from chronic antigenic stimulation and exhaustion, this add-on therapy perhaps can be considered in patients with high-risk CLL genetics, those who received multiple lines of CLL-related therapies, expressing T-cell exhaustion markers and 'slow' BTKi response where use of IgRT might pave the way to reduction in oligoclonality in T- and B-cells in the complex tumour microenvironmental niches.

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