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Use of Intravenous Immunoglobulin for Secondary Hypogammaglobulinemia Following Treatment in Waldenström's Macroglobulinaemia

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Introduction

Hypogammaglobulinemia is a common finding in Waldenström's Macroglobulinaemia (WM) and can persist despite WM treatment (1). B-cell and plasma-cell depleting therapies such as Rituximab, alkylating agents and BTK-inhibitors can also induce iatrogenic hypogammaglobulinemia and may increase the risk of developing infections (2). Intravenous immunoglobulin (IVIg) is used to reduce the risk and severity of infections for people with secondary hypogammaglobulinemia. It is only commissioned in United Kingdom if certain criteria are fulfilled. This includes having recurrent or severe infections despite prior vaccination against encapsulated bacteria, continuous antibiotic treatment and IgG concentration less than 4g/L (3).

Aim

Our objective was to describe the number of WM patients who required IVIg for managing recurrent infections due to hypogammaglobulinemia secondary to WM treatment.

Methods

Using our electronic patient records system at University College London Hospitals Trust (UCLH), we retrospectively reviewed the patients who received IVIg for secondary hypogammaglobulinemia due to treatment.

Results

We identified 474 patients diagnosed with WM in UCLH from 2004-2024 and had follow-up with our centre from 2018 onwards. 24/474 (5%) patients had IVIg following immunosuppressive therapy due to recurrent infections and hypogammaglobulinemia. Median age of these patients at WM diagnosis was 59 years (range: 37-76 years) and median follow-up from diagnosis was 127 months (range: 17-270 months). Recurrent respiratory infections were the most common indication for IVIg treatment (figure 1).

Out of the patients who received IVIg (n=24), 15 had 0.4g/kg IVIg every four weeks, one patient every six weeks with same dose, eight with unknown frequency (due to being treated at another centre) and three switched from IVIg to subcutaneous immunoglobulin (due to poor tolerance

to IVIg or preference) and given weekly. Four of the patients stopped regular IVIg due to reactions whilst the remainder are on continuous IVIg therapy till their latest follow-up.

The median time to IVIg initiation following first-line therapy was 35 months (range: 9-225 months). Most patients (38%) required IVIg after they received their first-line chemotherapy (figure 2). R-bendamustine (BR) was the most common treatment regime seen in patients requiring IVIg treatment and was given in 46% (figure 3).

Patients who required IVIg appear to have both low IgG and IgA antibody concentrations prior to starting IVIg. From the available data of IVIg patients, their median IgG was 2.14g/L (range: 0.9-3.92) and median IgA was 0.1g/L (range 0.1-1.13) prior to treatment initiation. Normal range of IgG concentration is 7-16g/L whereas IgA range from 0.7-4g/L. The trough immunoglobulin concentration following regular IVIg (value taken at least 12 months after initiation) was 9.21g/L for IgG (range: 1.92-13.81) and 0.29g/L (range: 0.1-1.43) for IgA, thus demonstrated no change in IgA concentration.

Conclusion

Our data confirms that clinically significant hypogammaglobulinemia affects a small proportion (5%) of patients with WM and requires significant ongoing medical intervention for ongoing benefit. Replacement with immunoglobulin can be effective in increasing IgG levels but does not appear to improve IgA levels, which may explain why some patients do not experience benefit from IVIg.

490words

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Figures

Figure 1. Table demonstrating the different types of recurrent/persistent infections which gave indication for IVIg therapy in secondary hypogammaglobulinemia in WM patients

Type of infections	Number of patients
Respiratory	20
Eyes, ear, nose and throat	4
Urinary tract infection	3
Skin	2
Other	2

Figure 2. Table showing the number of lines of WM treatment patient received prior to IVIg initiation

Number of lines of WM treatment received prior to IVIg initiation	Number of patients (n=24)
1	9 (38%)
2	7 (29%)
3	4 (17%)
4	2 (8%)
5	0
6	2 (8%)

Figure 3. Table showing treatment regimens used to treat WM in cohort who received IVIg

Treatment regime	Number of patients
BR	11
R-CHOP	7
BTKi	6
Rituximab monotherapy	5
DRC	5
Cladribine	3
Chlorambucil	3
Bortezomib	2
Fludarabine	2
Other	17