Hypogammaglobulinemia and response to therapy

We then sought to understand the relationship with response to therapy.

• We noted that very few patients’ hypogammaglobulinemia levels normalized completely, nor did their uninvolved paired isotype HLC levels normalize.

• However, we found that 55% of responders (IMWG) had improved levels (by at least 20%) of the uninvolved paired isotype HLC compared to 18.5% of the non-responders (p=0.001).

Similarly, an improvement of at least 50% in the levels of uninvolved paired isotype HLC was achieved by 35% of responders compared to 13% of non-responders, respectively (p=0.013);

An improvement of 75% was reached by 22.5% of responders and 7.4% of non-responders (p=0.028).

• This data strongly correlated to the depth of response, since 75% of patients in VGPR or better had improved levels of uninvolved paired isotype HLC by 50% at the time of greatest response, compared to 31% for PR and 13% for SD (p=0.005).

• Similar correlations were seen for patients that had improved levels by 20% (p<0.0001) and 75% (p=0.16) recoveries.

Introduction

The depth of Hypogammaglobulinemia has been related to adverse prognosis in myeloma for decades, but most importantly, it has been suggested that its recovery following treatment was associated with good outcome and prolonged survival.

However, none of the traditional techniques has allowed a precise measurement of isotype-matched (i.e. concentrations of IgGκ in an IgGα myeloma patient) hypogammaglobulinemia.

Recently, a new test quantifying paired clonal and non-clonal immunoglobulins (heavy/light chains HLC i.e. IgGκ/IgGα) in serum was developed. Here we aim to assess the new HLC assays as tools to measure Hypogammaglobulinemia, and potentially replace traditional techniques for the monitoring of patients with myeloma.

Material and Methods

107 (59 IgGκ, 29 IgGα, 12 IgAκ, 7 IgAα) myeloma patients treated with pomalidomide and dexamethasone in two IFM studies (IFM 2009-02 in end-stage RRMM, and IFM 2010-02 in del17p and t(4;14) RRMM) were included.

The criteria for selection were that patients had measurable intact immunoglobulin myeloma according to IMWG criteria (M spike ≥10g/L), using serum and/or urine protein electrophoresis, with exclusion of patients solely measurable on UPEP and sFLC.

All sera were collected centrally before initiation of treatment and sequentially every cycle until progression. Hevyllite® (HLC) was measured in the biology laboratory of CHRU of Lille (France).

For each patient we have measured the clonal isotype HLC level, and the corresponding non-clonal paired isotype HLC level, e.g. for IgAκ myeloma, the IgAα non-clonal paired isotype. (Normal ranges: IgGκ 3.84-12.07, IgGα 1.91-6.74 and IgGκ/IgGα 1.12-3.21; IgAκ 0.57-2.08, IgAα 0.44-2.04 and IgAκ/IgAα 0.78-1.94 g/L).

Results

Hypogammaglobulinemia characterizes Myeloma and persists overtime

• 98 (92%) patients had an abnormal suppressed uninvolved HLC level at baseline. Suppression was more common in IgGα than IgGκ patients (95% vs 73%, p<0.001)

• The median uninvolved IgGκ and IgGα HLC concentrations at baseline were 0.62 and 0.2 g/L respectively (range: 0.05-6.9; 0.01-5.6).

• 94 (87%) had an abnormal suppressed uninvolved HLC level at the time the best response was reached (IgG κ 90% > IgGα 77%). At best response, levels reached were 0.53 and 0.24g/L respectively (0.01-5.6; 0.01-7.4).

• Interestingly, more patients had recovered in the IFM 2010-02 study compared to the IFM2009-02 study. It should be noted that the studies differed in the number of prior lines of therapy (3 and 6, respectively).

• This data means that the vast majority of patients had not recovered from hypogammaglobulinemia at the time of best response in RRMM independently of early or late relapse or the refractory status.

Discussion

The mechanism of immunosuppression in myeloma patients is poorly understood.

Here we have shown for the first time that isotype-matched hypogammaglobulinemia correlates to depth of response.

Hypogammaglobulinemia is important to assess not only because of it leads to a greater risk of infectious complications, often severe in myeloma, but also as it plays a predictive role in occurrence of response and more importantly depth of response.

Future studies are needed to unravel the relationship between debulking of tumor cells and correction of hypogammaglobulinemia; in other words, is repopulating of the marrow with normal B cells associated to better outcome, and how does this affect the homeostasis of the bone marrow in its ability to support tumour cells.