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### On Waldenström's macroglobulinemia and IgM related disorders

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# Chapter 7

Summary, discussion and  
future perspectives



Waldenström Macroglobulinemia (WM) and IgM-related disorders have unique clinical features, pathophysiology and reactions to therapeutic agents. The research described in this thesis was conducted to gain insight into various manifestations of WM and IgM-related disorders, ultimately aiming to help improve diagnosis, therapy, and patient outcomes.

## BING NEEL SYNDROME

Bing Neel Syndrome (BNS) is a rare WM variant, defined as central nervous system invasion of LPL cells. **Chapter 2** evaluates fludarabine as a treatment option for BNS in a series of five consecutive cases. The nucleoside analogue fludarabine, combined with rituximab in all but one patient, led to a complete remission of the BNS and at least a partial remission of the WM in all cases. Three patients were still in remission after 1,5- 3,5 years of follow up. One patient relapsed 5 years after fludarabine treatment and responded again to rituximab-fludarabine. There were no grade 3 or higher toxicities with the exception of grade 3 reversible neutropenia in one patient. We concluded that fludarabine combined with rituximab is an effective and feasible treatment for BNS with a relevant duration of response. The efficacy of nucleoside analogues in BNS has since been confirmed in two large multicenter case series that together included 78 patients with BNS. Ten patients were treated with a nucleoside analogue based regimen, six reached a complete remission, two a partial remission, one had stable disease and one showed progressive disease.<sup>1,2</sup>

It is difficult to establish the position of fludarabine in the treatment of BNS. Since BNS is exceedingly rare, there is no standard of care and a benchmark is lacking.<sup>3</sup> The advantages of fludarabine are its oral availability and tolerability also in the elderly WM population, as well as the wide experience with this drug in the treatment of B-cell malignancies including WM. There are concerns about secondary malignancies after the use of nucleoside analogues although this was not confirmed in a recent large randomized trial in WM.<sup>4</sup> Whether more intensive therapy (for example high dose methotrexate or cytarabine) leads to longer lasting responses is currently unknown. Similarly, high dose therapy with autologous stem cell rescue or radiation therapy have been reported as effective treatments but curation has never been achieved. Whether these approaches lead to a better tradeoff between effects and side effects is unknown. The added value of rituximab in this context is also uncertain. In CNS large-cell lymphoma, the effect of rituximab is debated because of low CNS drug levels. Indeed, in a recent randomized trial in newly diagnosed PCNSL, the addition of rituximab to high-dose methotrexate based chemotherapy did not improve responses or outcomes, although follow up was insufficient to evaluate the effect on overall survival.<sup>5</sup> However, rituximab has added

value in WM without CNS involvement.<sup>6</sup> Since most patients with BNS also have systemic localization of WM, the use of rituximab therefore seems reasonable in this context. Finally, ibrutinib, a novel oral inhibitor of Bruton's Tyrosine Kinase (BTK) that is highly active in WM, is a promising treatment option for BNS. It is capable of passing the blood brain barrier, and has shown efficacy in BNS based on a handful of case reports<sup>7-9</sup> as well as in CNS involvement in other B-cell malignancies<sup>10,11</sup>.

Clearly, there is a high need for prospective trials in the field of BNS in order to clarify the optimal treatment approach. Nucleoside analogues and ibrutinib both seem attractive candidates for such trials because of their proven efficacy in WM, capacity to cross the blood-brain barrier as well as oral availability and tolerability. The latter is important in the mainly elderly population of WM patients. Also, both drugs have shown promising effect in BNS based on published case reports and small case series. Because of the low incidence of BNS, clinical trials in this field would need to be undertaken in a joint international effort.

## NEPHROPATHY RELATED TO WALDENSTRÖM'S MACROGLOBULINEMIA

**Chapter 3** describes a retrospective cohort study of 1391 WM patients, assessing biopsy-proven WM-related nephropathy. The estimated cumulative incidence of disease-related nephropathy was 5.1% during fifteen years of follow-up after the initial WM diagnosis. There was a wide variation in kidney pathology: AL amyloidosis, monoclonal-IgM deposition disease (MIDD)/cryoglobulinemia and LPL infiltration were the most frequent types of WM-related nephropathy. Light chain deposition disease (LCDD), cast nephropathy, thrombotic microangiopathy (TMA), minimal change disease, membranous nephropathy and crystal-storing tubulopathy (leading to acquired Fanconi syndrome) were also identified. The wide variation in WM-related kidney pathology was confirmed in a recent cohort study at the Mayo clinic<sup>12</sup>. The median overall survival was shorter in patients with WM-related nephropathy compared to the rest of the cohort and survival was shorter in patients that showed further decline of renal function after treatment. We concluded that monitoring for signs of renal disease is warranted in the follow up of WM patients and analysis of otherwise unexplained renal disease justifies a low threshold for a kidney biopsy in this setting. We also suggested that early detection of kidney disease and timely treatment might improve outcomes in patients with WM related nephropathy.

The three cases of renal TMA identified in this cohort were a novel finding, and illustrate the need to study large patient volumes to recognize rare complications of a rare disease. Since these three patients did not have the clinical characteristics of typical HUS, had no other explanation for the renal TMA and TMA activity coincided with WM diagnosis and relapse, we concluded that this can indeed be considered as a WM-related

nephropathy. Recently, it was confirmed that paraproteinemia has a higher prevalence in patients with TMA compared to the normal population again suggesting a pathogenetic link.<sup>13</sup> In this study, 20% of the paraproteins found in TMA patients were of the IgM isotype. We propose several explanatory mechanisms: WM patients are known to have an elevated risk of venous thrombosis, are prone to hyperviscosity syndrome and have elevated von Willebrand factor levels; the paraprotein may act as an antiphospholipid antibody; interactions of the paraprotein or tumor cell with the local renal microvasculature or the complement system could contribute to a prothrombotic state.

Based on our study we could not reach a conclusion about the optimal treatment of WM related nephropathies: the number of cases per group of renal pathology was too small and the applied treatment regimens were too heterogeneous. The association of deep hematological responses with better outcomes was already known for AL amyloidosis in general, and recent publications have confirmed this for monoclonal IgM-related AL amyloidosis and LCDD.<sup>14,15</sup> In WM patients with renal AL amyloidosis and LCDD, reaching a deep hematological response (very good partial remission or complete remission) should therefore be the explicit goal of treatment. Several agents could be used as the backbone for immune-chemotherapy induction, but there are no data supporting one specific treatment approach<sup>16</sup>. Based on the AL amyloidosis and LCDD literature, consolidation with high dose chemotherapy and autologous stem cell transplantation should be strongly considered in fit patients with those conditions since this seems associated with the longest and deepest responses. The role of rituximab maintenance in this setting has not been studied, but since it has been found to be associated with much longer PFS (6.8 with rituximab maintenance versus 2.8 years without it, however only in a retrospective study could be an option worth exploring.<sup>17</sup>

Little is known about the optimal approach in the other WM-related nephropathies. There are no studies on the optimal treatment of WM-related MIDD, cryoglobulinemia, cast nephropathy, minimal change disease, membranous nephropathy, TMA, acquired Fanconi syndrome and LPL infiltration of the kidney and it is unknown whether the association of deep responses with clinical outcomes is also true in these diseases.

Ideally, clear guidelines would be developed on the optimal approach to each type of WM-related nephropathy and the optimal timing of initiation of treatment in order to save kidney function and improve overall survival. Realistically, these are rare manifestations of an already rare disease and it is unlikely that prospective trials will ever be done for every type of WM related nephropathy. Large retrospective case series might be the only way to shed more light on the various types of WM nephropathy, their clinical presentation, prognosis and response to therapy.

## IGM ANTI-MAG PARAPROTEIN-ASSOCIATED PERIPHERAL NEUROPATHY

IgM paraproteinemia in patients with IgM MGUS, WM or other B-cell malignancies can be associated with a range of peripheral neuropathies (PN): IgM related peripheral neuropathies. There is a wide spectrum of disease ranging from the most prevalent type, anti-MAG neuropathy to AL amyloidosis, POEMS syndrome and the exceedingly rare CANOMAD syndrome. Diagnosis and management can be very challenging due to variations in clinical presentation and the lack of data on optimal treatment. **Chapter 4** describes a consensus approach based on the 8<sup>th</sup> International Workshops on WM regarding diagnostic workup, outcome parameters and models of care including treatment recommendations. We concluded that clinical trials of novel therapies are urgently needed in this setting since most recommendations are now made based on expert opinion and consensus instead of evidence. The use of reliable neurological outcome criteria are essential for these clinical trials, and the I-RODS scale is suggested for future validation and use in the field of anti-MAG PN.<sup>18,19</sup>

IgM related disorders are unique because they have features of cancer as well as auto-immune disease: very few monoclonal and therefore (pre)malignant cells produce a small amount of paraprotein that causes a large amount of damage, often via immune responses to self-antigens. Interestingly, not all IgM related disorders seem to have the same biology as WM. Cold agglutinin disease (CAD) is an auto-immune hemolytic anemia typically caused by monoclonal IgM antibodies directed against the I antigen on erythrocytes. In CAD, MYD88<sup>L265P</sup> is mostly absent, and a distinct pattern of immunoglobulin heavy chain variable (IGHV) gene usage is seen different from that in WM.<sup>20,21</sup> This suggests that CAD is biologically different from and should not be considered to be a variation of WM.

It was in this context that we were interested in the pathogenetic link between WM and anti-MAG peripheral neuropathy. **Chapter 5** contains a study on the prevalence of MYD88<sup>L265P</sup> in the bone marrow of anti-MAG PN patients. MYD88<sup>L265P</sup> was found in 12 of 20 anti-MAG PN patients (60%). Our results establish that, in line with asymptomatic IgM MGUS and WM, the majority of anti-MAG PN cases carry MYD88<sup>L265P</sup>. We conclude that our findings point towards a shared pathophysiology between WM and anti-MAG PN. Our data were recently confirmed in a French cohort of 26 anti-MAG patients with a prevalence of MYD88<sup>L265P</sup> of 73%<sup>22</sup>. Additionally, this study analyzed the IGHV sequence of the clonal B cells. They found a high frequency of VH3 segment usage in anti-MAG PN, WM and IgM MGUS patients, again suggesting a shared pathophysiology.

This shared biology is relevant considering the high clinical need for effective therapy in anti-MAG PN and the challenges in initiating meaningful clinical studies in this field. Our data support the initiation of clinical trials for anti-MAG PN using agents that have proven efficacy in WM, specifically novel oral agents with little (neuro-) toxicity such as

the BTK inhibitors or second-generation proteasome inhibitors. Consensus-based disease definitions and response criteria should be used to optimally document the effect on neuropathy-related endpoints. Again, international collaboration is probably necessary to reach sufficient inclusion in a reasonable amount of time.

## WM, CYTOKINES, CHEMOKINES, HEPCIDIN AND IBRUTINIB

**Chapter 6** features the results of a study on biomarkers (hepcidin, multiple cytokines and chemokines) in WM, in relation to molecular subtype and to ibrutinib therapy.

### Anemia & hepcidin

Hepcidin is a key regulator of iron metabolism and known to be produced by LPL cells<sup>23</sup>. When the hepcidin level is abnormally high, serum iron falls and hemoglobin drops. Ibrutinib leads to a surprisingly fast resolution of anemia in WM patients, discrepant to the rather slow and incomplete decrease in bone marrow tumor load<sup>24</sup>. We hypothesized that ibrutinib might suppress hepcidin, explaining the rapid increase in hemoglobin. Although there was a subtle decrease of hepcidin levels after ibrutinib treatment, hepcidin changes did not correlate with changes in hemoglobin or markers of iron metabolism. We concluded that the resolution of anemia is not explained by effects on hepcidin. It might be related to another immunological effect perhaps related to IgM itself.

### Cytokines and chemokines in WM

The levels of several cytokines and chemokines were found to be elevated in the plasma of WM patients compared to healthy donors, confirming previous data.<sup>25</sup> However, the high levels of CXCL13 in WM patients were a novel finding. We identified subtle differences in cytokines and chemokines based on molecular subtype, although these signals were not strong enough to make cytokine-based profiles using principal component analysis. The fact that several cytokine levels were lower in MYD88<sup>L265P</sup>CXCR4<sup>MUT</sup> versus MYD88<sup>L265P</sup>CXCR4<sup>WT</sup> patients may relate to the suppression of MYD88<sup>L265P</sup> induced inflammatory pathways in MYD88<sup>L265P</sup>CXCR4<sup>MUT</sup> patients as described in a transcriptome study.<sup>26</sup> The lack of a separate cytokine profile in MYD88<sup>WT</sup>CXCR4<sup>WT</sup> might be related to the small number of patients or the heterogeneity of this subgroup.<sup>26</sup> We found strong effects of ibrutinib on inflammatory cytokine and chemokine levels, paralleling changes observed in CLL patients on ibrutinib therapy.<sup>27</sup> These changes may be related to on-target tumor effects leading to decreased cytokine production by LPL cells and/or the impact of ibrutinib on microenvironmental cells such as T cells or macrophages. Interestingly, only CXCL13 was a predictor for major response, and post-treatment changes in CXCL13 levels showed a strong correlation to response.

### CLXCL13

During a normal immune response, activated follicular T-helper cells produce CXCL13, leading to chemotaxis of cells with the CXCL13 receptor CXCR5, including B cells and certain T-helper cells, attracting them to the follicle to take part in the germinal center reaction. In addition, CXCL13 can be produced by cells of myeloid lineage (monocytes and macrophages).<sup>28</sup> Transcription of CXCL13 has also been demonstrated in LPL cells<sup>26</sup>. In our study, CXCL13 levels strongly correlated to hemoglobin levels and the extent of BM infiltration in WM patients. These correlations were also seen at a transcriptional level<sup>26</sup>. CXCL13 was strongly suppressed after ibrutinib therapy in WM patients, similar to what was seen in an ibrutinib trial in CLL<sup>27</sup>. CXCL13 was the only cytokine that predicted a major response to ibrutinib: a high CXCL13 level at baseline was a strong predictor for achieving a partial response or better. Major responses were accompanied by a deep suppression of CXCL13 levels. As far as we know, there are no published data on the qualities of CXCL13 as a predictor of response to BTK inhibition in other B-cell malignancies. We concluded that these data support a role of CXCL13 in WM biology. Our data justify further exploration of the role of CXCL13 in WM pathophysiology including sensitivity to ibrutinib treatment. The value of CXCL13 in predicting the response to BTK inhibition needs confirmation in WM and exploration in other B-cell malignancies. Also, it remains to be unraveled where the excess CXCL13 is produced: LPL cells or microenvironmental cells such as T-cells or macrophages? Finally, the mechanism behind the correlation between CXCL13 levels and anemia and BM infiltration, both clinical hallmarks of WM, remains unknown.

### GENERAL DISCUSSION

**In conclusion**, this thesis illustrates the challenges of establishing the optimal care for rare manifestations of an already rare disease. How should we best treat anti-MAG neuropathy (and other, even rarer variants of IgM related neuropathy), all the different types of WM related renal disease, or Bing Neel Syndrome? Large randomized clinical trials will most likely never be conducted in these rare disease manifestations. The way forward probably is to be found in (inter)national collaboration, translational research to identify optimal candidate drugs for clinical trials and biomarkers to identify the right patients for them, and patient registries to learn about disease characteristics, dynamics and responses to treatment.

Considering how rare these conditions are, it is crucial to facilitate optimal inclusion of patients in these clinical databases, biobanks and clinical trials. Innovative approaches, where patients can be treated in their local facility but remain to have access to the ex-

expertise and research possibilities of an expert center, need to be explored. WM patients' organizations have been instrumental in setting up novel ways of doing this and inspiring examples are being set worldwide. In Australia, the "WhiMSICAL" study, initiated in collaboration with the Australian WM patient association "WMozzies", allows WM patients worldwide to register online and fill out questionnaires about their disease.<sup>29,30</sup> A similar project called the Rory Morrison Registry is run by the WMUK (the UK charity for MW), allows patients to register and data to be entered via their treating physician.<sup>31</sup> At the Dana Farber Cancer Institute in Boston, the PCROWD study allows patients to register online and submit their tissue or blood samples via a kit that they can bring to their own local hospital.<sup>32</sup> The development of online tools to bring patients, physicians and researchers together is promising in rare diseases including WM and all its different manifestations including IgM-related disorders.

This thesis also illustrates the wide-ranging clinical presentation of WM and IgM-related disorders. Physicians should monitor all organ systems during initial evaluation and follow up of not only WM patients, but also individuals with IgM MGUS. An interdisciplinary approach is highly recommended to come to a correct diagnosis and optimal treatment plan for those patients with "non-hematological" disease manifestations such as nephropathy, neuropathy and Bing Neel syndrome. Also, a web-based system for physician-to-physician consultation might facilitate sharing of knowledge in these often challenging cases.

**Looking outside the scope of this thesis and into the future**, it is very promising that the field of WM has been so active in recent years. As mentioned in the introduction, the major breakthroughs were molecular studies, including the discovery of highly prevalent somatic MYD88 and CXCR4 mutations, and the introduction of ibrutinib a new benchmark for therapeutical studies.

But this does not mean that work in WM is done. On the contrary, these discoveries have set the stage for further unraveling of WM pathophysiology and optimal treatment. Currently, WM is still an incurable disease. Fortunately, many novel agents with potential in the treatment of WM are becoming available. Clinical trials are ongoing or being developed for (combinations of) BCL2 inhibition, anti-CD38 antibodies, novel anti-CD20 antibodies, CXCR4 inhibition, novel BTK inhibitors and novel proteasome inhibitors including the role of maintenance therapy. An agent targeting the MYD88/IRAK-NFKB pathway is not clinically available at this moment, but an inhibitor of IRAK1 kinase activity is being developed and has activity in WM cell lines.<sup>33</sup> These novel targeted therapies allowing for a "chemo-free" approach are also promising in the treatment of IgM-related disorders, where clinicians are reluctant to initiate traditional chemotherapy in a disease that is not considered to be cancer.

In an ideal future we will be able to individualize patient care: characterizing the type of WM (based on molecular characteristics and biomarkers), the type of disease manifestation (based on meticulous clinical evaluation including multidisciplinary collaboration when needed), the type of patient (age, comorbidities, frailty, personal preferences) and the expected response to various agents (based on (molecular) biomarkers) would lead to the desired level of response (disease control with alleviation of symptoms only or a deep/complete remission) and an individualized treatment plan.

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