Waldenstrom macroglobulinemia: new treatment options for relapsed disease: results from IWWM9!

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Treatment of relapsed WM
Treatment of relapsed WM in 2016

- **No signs/symptoms**: wait and see
- **If treatment is indicated**: look at:
  - Response to prior treatment (retreat)
  - Age
  - Fitness/comorbidity
  - Bone marrow reserve (cytopenia)
  - IgM level (flare)
  - Rapid control necessary?
  - Stem cell toxicity?
  - Side effects (neuropathy)
Choice of Therapy by Line of Treatment in the Overall Population
(n=368 patients European retrospective study (dr Buske))
New treatment modalities (background)

- **(New chemotherapy)**
- **New monoclonal antibodies**
  - Directed at other proteins on the WM cell (e.g., immune checkpoint, CD38)
  - Antibody drug conjugate (radioisotope or chemotherapeutic)
  - Bispecific antibodies
  - CAR-T cells
- **Interaction with microenvironment**
- **Better understanding of what goes wrong in the tumor cell (signalling)**
Mechanisms of action of antibodies

Novel antibodies
- Second generation CD20 antibodies
- Other targets, eg CD38, immune checkpoints
  - Bispecific antibodies
  - Radioimmunotherapy
- Antibody-drug conjugate (ADC)
- CAR-T cells

radionuclide $\rightarrow$ cytostaticum
CD20 Expression during B-cell development

- Bone marrow
- Blood, lymph nodes

Pluripotent stem cells → Lymphatic stem cell → Pre-B cell → B cell → Act. B cell → Plasmacell

CD20

CD38
sCD27 in WM-Mast Cell Interactions

Alemtuzumab

CD70

SGN-70

CD52

TACI, BCMA

C-kit

Imatinib mesylate

MMP-8

CD27

Mast cells

Lymphoplasmacytic cells

CD40L

CD40

APRIL

**Daratumumab: Mechanism of Action**

- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity\(^1\)-\(^5\)
- Depletes CD38\(^+\) immunosuppressive regulatory cells\(^5\)
- Promotes T-cell expansion and activation\(^5\)

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Activating your own immune system

- Patient’s immune cells (T cells) can recognize tumor cells
- These T cells are on a brake

Breakthrough of the Year 2013
Immune system ‘checkpoint’ = brakes:
PD-L1 tumor cells/PD-1 T cells
Bi-specific antibodies: Blinatumomab: they direct the T cell to the tumor cells
Chimeric Antigen Receptor T cellen (CAR-T cells)

- CAR-T cells combine an antibody specific for tumor cells with properties of T cells (chimeric)
- With the help of a virus the chimeric receptor is transferred to the T cells

Courtesy Dr Gribben
T cells isolated from patient

Introduction CAR proteins via virus or other system in T cells

CAR T cells

Expansion

Chemo/radiotherapy: lymfocyte depletion

Infusion in patiënt

10 days
CAR-T cells

- Thus far more experience in acute leukemia, aggressive NHL
- Only a few WM patients
- Toxicity:
  - cytokine release storm (ICU)
  - Neurologic symptoms
  - B cell depletion
- Increase efficacy
- ‘On-off’ switch?
- Better understand/prevent toxicity
Normal cell division

Tumor growth
Central: NFkB activation → proliferation
Inhibition cell death
NHL: Targeted therapy: focus on pathways
Younes Nat Rev Oncol 2012

- **ibrutinib**
- **bortezomib**
- **PKC-inh**
- **idelalisib**
- **temsirolimus**
- **P13K**
- **AKT**
- **ARD**
- **STAT**
- **NF-κB**
- **CD79A**
- **P**
- **Gene regulatory proteins**
- **Other target proteins**

**Key pathways**:
- Cytokine receptor
- IL-6, IL-10
- BCR
- BAFF, CD40L, TNF-α
- TNF/SFR
- VEGF
- Receptor tyrosine kinase
- JAK1, JAK2, Lyn, Syk, BTK
- PKC
- MAPK
- mTOR

**Drug targets**:
- **ibrutinib**
- **bortezomib**
- **PKC-inh**
- **idelalisib**
- **temsirolimus**
HOVON124 study

- First HOVON study MW!
- For patients with relapsed WM
- New oral proteasome inhibitor ixazomib in combination with rituximab and dexamethasone
- Followed by 2 years of rituximab maintenance
- Oral, less neurotoxic
- HOVON (NL), Belgium and Greece
- Ongoing
Ibrutinib

- Phase II study dr Treon (3 centres USA)
- 63 patients
- 420 mg ibrutinib until progression
- Response: 91% (no complete responses)
- IgM 3.2 → 1.2 g/dl
- Hematocrit 31 → 39.7%
- BM infiltration 70 to 40%

- LONG TERM FOLLOWUP (dr. Palomba)
Long-term follow-up (median f/u 37 months)

- 25/63 patients stopped, 11 because of progression
- 3 year event-free survival 68%; overall survival 90%
- Few new side effects with longer follow up (especially cardiac or bleeding)
- 3/6 tested progressive patients had mutations in btk or ‘downstream’
New Btk inhibitors

- New btk inhibitors
  - Acalabrutinib
  - BGB-3111
  - ONO

- Combinations with other drugs
MYD88 signaling:
BTK, IRAK inhibitors, HCK
Why target Bcl-2 in WM?
Best Percent Change From Baseline SPD Nodal Mass by CT

As of September 15, 2015

Davids et al., 2016 (in revision)
Is venetoclax safe and effective in patients with NHL?
Phase I/II Study of Venetoclax in Previously Treated WM

Screening/Informed Consent/Registration

Venetoclax 200mg ➔ 800mg daily

Progressive Disease or Unacceptable Toxicity

Stop venetoclax

Event Monitoring

SD or Response
Continue

Event Monitoring
Stem cell transplantation

| **Autologous:** | own stem cells |
| **Allogeneic:** | donor stem cells |

Only a small percentage of patients is eligible (very young, fit, unresponsive to other treatments)
Conclusions

• Lots of new and hopeful developments
• More knowledge of the biology of the disease is crucial →
• New targets for treatment
• More possibilities for treatment in the context of clinical trials
• In the Netherlands:
  ∗ HOVON124 (ixazomib)
  ∗ BGB-3111 vs ibrutinib (phase III)
• Collaboration enormously important:
  ∗ With other countries (ECWM)
  ∗ With patient organizations (Hematon, EWMN, IWMF)
Future...

"Targeted therapy"

Treatment adjusted to patient/disease