WM: Managing the Side Effects of Treatment

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Jeffrey V. Matous, MD
Colorado Blood Cancer Institute
www.bloodcancerinstitute.com
Tampa, FL
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Determining a “side effect” in WM can be very tricky

• Many problems which WM patients experience from the disease are very similar to and overlap with some treatment side effects

• So let’s briefly review two subjects:
  – What are some symptoms of WM which can mimic treatment side effects?
  – How do we define “side effects” of treatment, that is, what do we need to report to our doctors and nurses?
WM symptoms

 Constitutional Symptoms

• There are certain recurring problems that physicians find in WM patients:
• Tiredness, usually the result of anemia
• Night sweats
• Headaches and dizziness
• Various visual problems
• Pain, numbness, or tingling in the extremities
• Abnormal bleeding from the nose and gums
• Enlarged lymph nodes, spleen, liver
Manifestations of WM Disease

- Adenopathy, splenomegaly ≤20%
- Fatigue, Sweats
- Cytokininemia?
- Low HCT, PLT, WBC
- Hyperviscosity Syndrome:
  - Epistaxis, HA, Impaired vision >4.0 CP
- IgM Neuropathy (22%)
- Cryoglobulinemia (10%)
- Cold Agglutinemia (5%)
Other Potential WM Problems

- Peripheral Neuropathy
- Retinopathy
- Anemia
- Hyperviscosity
- Cold Agglutinin disease
- Cryoglobulinemia
- Amyloidosis
“Side effect” definition: the view of the FDA

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

• The Point: Report any bothersome problem to your doctor and nurse and let us sort it out. Communicate. We do not read minds well.
• My lymphoma mentor (Dr. Oliver Press): “If you have something now and did not have it before, we probably did it to you”
Communication with your team is critical

- Keep a journal or notebook - do not trust your memory
- Even if you are not sure a problem is related to your treatment ask your doctor or nurse
- Once you know what your treatment will be ask for written information on potential side effects - and how to manage them
What is Chemotherapy?

- It depends who you ask!
- I define it, loosely, as any substance we put in our body to try and kill cancer cells
- Types of chemotherapy are changing, and the side effects from treatments are quite different one from the other
Approval Of Anticancer Drugs

"old school chemo"

Doxorubicin, vincristine, cyclophosphamide + prednisone = CHOP

Figure 2–1 Acquisition of new anticancer drugs since 1940. (Modified from Krakoff.43)
Increasingly Chemo looks like this
Let’s Consider Various Chemotherapies for WM

NCCN Guidelines Version 1.2014
Waldenström’s Macroglobulinemia/
Lymphoplasmacytic Lymphoma

SUGGESTED TREATMENT REGIMENS
(Order of regimens is alphabetical and does not indicate preference)

Primary Therapy:

Non-stem cell toxic
- Bortezomib ± rituximab
- Bortezomib/dexamethasone
- Bortezomib/dexamethasone/rituximab
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab
- Rituximab
- Rituximab/cyclophosphamide/prednisone
- Rituximab/cyclophosphamide/dexamethasone
- Thalidomide ± rituximab

Possible stem cell toxicity and/or risk of transformation (or unknown)
- Bendamustine ± rituximab
- Cladribine ± rituximab
- Chlorambucil
- Fludarabine ± rituximab
- Fludarabine/cyclophosphamide/rituximab

Salvage Therapy:

Non-stem cell toxic
- Alemtuzumab
- Bortezomib ± rituximab
- Bortezomib/dexamethasone
- Bortezomib/dexamethasone/rituximab
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab
- Everolimus
- Ibrutinib
- Ofatumumab (for rituximab-intolerant individuals)
- Rituximab
- Rituximab/cyclophosphamide/prednisone
- Rituximab/cyclophosphamide/dexamethasone
- Thalidomide ± rituximab

Possible stem cell toxicity and/or risk of transformation (or unknown)
- Bendamustine ± rituximab
- Cladribine ± rituximab
- Chlorambucil
- Fludarabine ± rituximab
- Fludarabine/cyclophosphamide/rituximab

Stem cell transplant
- In selected cases stem cell transplantation may be appropriate in either:
  - High-dose therapy with stem cell rescue
  - Allogeneic stem cell transplant (ablative or nonablative)
Did you notice how often we use rituximab?

**Primary Therapy:**

**Non-stem cell toxic**
- Bortezomib ± rituximab\(^1,2,3,4\)
- Bortezomib/dexamethasone\(^3,4\)
- Bortezomib/dexamethasone/rituximab\(^1,2,3,4\)
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab\(^1,4\)
- Rituximab\(^1\)
- Rituximab/cyclophosphamide/prednisone\(^1\)
- Rituximab/cyclophosphamide/dexamethasone\(^1\)
- Thalidomide ± rituximab\(^1,4\)

**Possible stem cell toxicity and/or risk of transformation (or unknown)**
- Bendamustine ± rituximab\(^1\)
- Cladribine ± rituximab\(^1,5,6\)
- Chlorambucil\(^5,6\)
- Fludarabine ± rituximab\(^1,5,6\)
- Fludarabine/cyclophosphamide/rituximab\(^1,5,6\)
Some side effects are common to most treatments, but some are unique to certain treatments

- Before you start on any treatment your doctor and nurse should discuss with the potential risks and benefits of the treatment
- This always happens when you are treated on a research study or clinical trial but should happen with every treatment
- This is called “Informed Consent”
Common chemo side effects

- Nausea or vomiting
- Constipation
- Diarrhea
- Low blood counts
- Hair loss (sometimes)
- Fatigue
- “Chemo brain”
Rituxan side effects

- “flare”
- “infusional reactions” (patients often say “allergic”)

IgM flare occurs following Rituximab therapy including combination therapy in patients with Waldenstrom’s Macroglobulinemia.

IgM flare rates reported with Rituximab therapy

- Monotherapy (40-60%)
- Fludarabine/Rituximab (40%)
- Cyclophosphamide/Prednisone/Rituximab (25-30%)
- Thalidomide/Rituximab (50%)
- Lenalidomide/Rituximab (75%)
- Bortezomib/Dexamethasone/Rituximab (9%)

Denotes patient underwent plasmapheresis at this time point for hyperviscosity.

“Rituxumab Flare”

FIGURE 1. Serially measured immunoglobulin M (IgM) levels in patients who experienced an initial IgM ‘flare’. Twenty-nine patients (54%) experienced an increase in IgM levels between baseline and Time Point 1. By Time Point 4, however, 11 of the 15 patients for whom data were available (73%) had IgM levels that were below baseline levels.

WM patients more frequently do not tolerate Rituxan

- Rituxan can produce allergic reactions while infusing
- Premedications are always given - usually benadryl & tylenol
- Non WM: rare it cannot be given successfully
- 1/6 WM patients no matter what we do just cannot tolerate it
- Tricks of the trade: more aggressive premedication (steroids), longer infusions, break up the dose
- Can try ofatumumab
#1: Fatigue

- Toughest symptom: most common for WM and for WM treatments!
- Exercise
- Rest, but not too much
- Should improve with control of disease, but...
- Cumulative chemo side effects can also worsen fatigue
Nausea

- Much less of a problem
- Great medicines to prevent and/or treat
- Many patients do not optimally take nausea prevention drugs
Other gastrointestinal side effects

- We are good at messing up the bowels
- Diarrhea
- Constipation
- Acid reflux
Infections

• WM patients have an increased risk of infections anyway, and chemo can further increase the risk
• Low levels of naturally occurring antibodies
• Steroids
• Low white blood counts
• Certain drugs increase the risk of shingles
Infections: What to do?

• Vaccinations: flu shot yes, be very careful with live virus vaccinations such as the shingles vaccine
• Common sense: wash hands, sick contacts

• IvIg infusions- not needed very often
• Know your white blood count
• Lower threshold to use antibiotics
Leg Cramps

- L glutamine
- Tonic water before bedtime?
- Bar of soap bottom of bed?
- OTC remedies
Peripheral Neuropathy

• Tough one
• Careful with chemo drugs that cause it (Bortezomib, vincristine, thalidomide, etc)
• Modern day alchemy trying to manage it
• Keep trying different things
Neuropathy, continued

• Non Rx things: vitamins (B6, B12, folate), supplements (alpha lipoic acid, glutamine)
• Rx: gabapentin, pregabalin,
• Old depression meds: amitryptilene, duloxetine
• Analgesics, even narcotics
• Real challenging problem
Anxiety & Depression

• Common
• Steroids worsen it
• Lots of help and support out there
• Many people benefit from prescription meds
Thank you!

• To the patients
• To the IWMF
• To Megan Andersen NP
• All the WM researchers around the world