Rituxan Maintenance vs. No Maintenance

No maintenance is needed if you respond well initially

Stephen Ansell, MD, PhD

Mayo Clinic
You don’t need Maintenance Rituximab if -

• You get chemotherapy + rituximab as initial treatment and respond well to treatment
• You want to avoid complications
• You want less visits to the doctor
• You want less cost

Maintenance therapy does not make patients live longer
Maintenance rituximab after chemoimmunotherapy improves the time you’re in remission – but not how long you live

Maintenance rituximab or observation after bendamustine-rituximab

**Complete Response**

**Partial Response**
Maintenance rituximab or observation after bendamustine-rituximab –
Incidence of toxicity and death
DEBATE
MAINTENANCE RITUXIMAB
IN WALDENSTROM MACROGLOBULINEMIA: YES OR NO? OBVIOUSLY YES!!!!

Morton Coleman, M.D.
Director, Center for Lymphoma & Myeloma
Clinical Professor of Medicine
Weill Cornell Medicine
Attending, New York-Presbyterian Hospital
Chairman, Medical Affiliates Board
Lymphoma Research Foundation
WALDENSTROM MACROGLOBULINEMIA AIN’T (IS NOT) LYMPHOMA
HOW MANY IN THE AUDIENCE HAVE AN ONGOING COMPLICATION FROM WALDENSTROM MACROGLOBULINEMIA?

NEUROPATHY
ANEMIA, NEUTROPENIA, THROMBOCYTOPENIA (MARROW REPLACEMENT, IMMUNE, HYPERSPLENISM)
HYPERVERSICOSITY, THROMBOSIS, AMYLOID OTHER—INFECTION, ETC.
AT LEAST 50% OF PATIENTS WILL HAVE A COMPLICATION FROM WALDENSTROM MACROGLOBULIN

IF YOU RESPOND, ARE YOU WILLING TO WAIT FOR THE SYMPTOMS TO RECUR AND/OR BE EVEN MORE SEVERE COMPOUNDING PRIOR DAMAGE TO YOUR NERVE OR BLOOD CELLS?

ARE YOU NUTS?
EVEN IF MAINTENANCE DOES NOT PROLONG LIFE, THERE IS THE MAJOR ISSUE OF QUALITY OF LIFE.

RITUXIMAB-BASED MAINTENANCE THERAPY IN WM: A CASE CONTROL STUDY
ASCO PRESENTATION 2019
Zanwar, Abeykoon, Gertz, Kumar, Witzig, Habermann, Rajkumar, Dispenzieri, Kyle, ANSELL, et al.
CONCLUSION: Maintenance demonstrated a trend toward a longer time to next treatment and a significantly longer overall survival!*
*thank you Pete Denardis
NOTHING IN LIFE IS BLACK AND WHITE, THERE ARE SHADES OF GREY.

STEVE IS NOT ALTOGETHER WRONG.

MAINTENANCE INCREASES THE INCIDENCE OF INFECTION AND MAY BE MORE EXPENSIVE.

THERE ARE INSTANCES WHEN THE PATIENT IS NOT TOO SYMPTOMATIC AFTER TREATMENT IN WHOM IT IS SAFE TO WATCH AND WAIT.

GET A DOCTOR WHO IS CARING AND KNOWLEDGEABLE IN WM AND MAKE A DECISION TOGETHER ON MAINTENANCE.
THANK YOU FOR YOUR ATTENTION
Fixed Duration vs Continuous Treatment Debate for Waldenstrom’s Macroglobulinemia

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Professor of Medicine
Abramson Cancer Center
University of Pennsylvania
Philadelphia, Pa

2019 IMWF Educational Forum
June 8, 2019
Fixed duration therapy is very effective and well tolerated

BR (bendamustine IV 90 mg/m² day 1,2 and rituximab IV 375 mg/m² on day 1 of each cycle, administered every 28 days)

The preferred approach is to use BR for a total of four to six 28-day cycles. Rituximab can be held during the first cycle to decrease the likelihood of a IgM flare.

High response rate: 80-90%.

Long remission duration: 6 years average

Well tolerated: very little hair loss, less than 1/3 have significant low blood counts, infections, mouth sores, rashes

Maintenance rituximab (every 3 months for 2 years) optional
Fixed duration therapy is very effective and well tolerated

BDR was administered as a single 21-day cycle of bortezomib alone (1.3 mg/m² IV on days 1, 4, 8, and 11) for cycle 1. Cycle 2 to 5 comprised of weekly intravenous bortezomib (1.6 mg/m² on days 1, 8, 15, 22 x 4 35-day cycles) with intravenous dexamethasone (40 mg) and intravenous rituximab (375 mg/m²).

The preferred approach is to use BDR for a total of four to six 28-35-day cycles. Subcutaneous administration of bortezomib preferred to reduce neuropathy.

High response rate: 80-90%.

Long remission duration: 4-5 years average.

Well tolerated: but up to 50% neuropathy.
Continuous therapy is very effective and well tolerated

Oral ibrutinib (420 mg once daily) until disease progression or unacceptable toxic effects. In the clinical trial, they also received intravenous rituximab (375 mg per square meter of body-surface area, with infusions at weeks 1 to 4 and 17 to 20)
Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström’s Macroglobulinemia

A Best Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Ibrutinib–Rituximab</th>
<th>Placebo–Rituximab</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>23</td>
<td>1</td>
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<tr>
<td>Partial response</td>
<td>47</td>
<td>27</td>
</tr>
<tr>
<td>Minor response</td>
<td>15</td>
<td>1</td>
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B IgM Levels

30-month PFS: 82%

Dimopoulos et al. N Engl J Med 2018
Is ibrutinib-rituximab better than ibrutinib alone?

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib +</th>
<th>Ibrutinib</th>
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<th>Ibrutinib</th>
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<tbody>
<tr>
<td></td>
<td>rituximab</td>
<td>relapsed</td>
<td>INNOVATE</td>
<td>frontline</td>
</tr>
<tr>
<td>N prev untreated</td>
<td>34</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>N prev treated</td>
<td>41</td>
<td>63</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>ORR</td>
<td>92%</td>
<td>91%</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>MRR</td>
<td>72%</td>
<td>73%</td>
<td>71%</td>
<td>83%</td>
</tr>
<tr>
<td>VGPR</td>
<td>23%</td>
<td>27%</td>
<td>13%</td>
<td>20%</td>
</tr>
<tr>
<td>PFS</td>
<td>30-mo: 82%</td>
<td>60-mo: 60%</td>
<td>18-mo: 86%</td>
<td>18-mo: 92%</td>
</tr>
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Potential Toxicities of Prolonged Ibrutinib

The substantial responses seen with ibrutinib therapy do come at the cost of unique toxicities.

Atrial fibrillation (AF) is a common complication with ibrutinib therapy, grade 3 or more AF can be seen in 10–12% of patients, often requiring dose reduction or permanent discontinuation.

Hypertension has also been described as a notable complication of ibrutinib therapy in 5–10%.

Major hemorrhages have been noted with ibrutinib, but they are uncommon and seen in fewer than 5% of cases.

A ‘rebound phenomenon’ that results in a rapid rise in serum IgM levels one-third after abrupt stopping ibrutinib
Comparison of Fixed Duration vs Continued Therapy for WM

**Ibrutinib advantages**
- oral formulations.
- Less traditional chemotherapeutic side effects like nausea, vomiting and profound low blood counts.

**Ibrutinib pitfalls**
- Other important toxicities.
  - atrial fibrillation and hypertension, which may pose a challenge, particularly in older patients who make up the predominant population in this disease.
- The need for continuous therapy.
- Lower efficacy in patients MYD88WT or CXCR4MUT genotype.
- Significant financial implications. >$100,000/year indefinitely.
- The abrupt discontinuation of ibrutinib can be associated with a rebound increase in IgM, something that is not observed with traditional chemoimmunotherapy approach.

**Chemoimmunotherapy (BR BDR) advantage:**
- Typically given for a fixed duration of 4–6 months.
- Providing a treatment-free interval for patients.
- If the disease progresses can then do ibrutinib with great success.

**Chemoimmunotherapy (BR BDR) pitfall:**
- Side effects like nausea, vomiting and profound cytopenias are more common than with ibrutinib.
- Increased risk of myelodysplastic syndrome in the future.
So what is the ‘best’ treatment?

Both approaches work great in terms of high response rates, long remissions and long life.

Real differences between them is the **duration of therapy, routes of administration and toxicity profiles of the regimens**.

The decision for choosing frontline therapy is based on
1) The presence of comorbidities (other medical problems)
2) The genotype (primarily the MYD88 genotype, with some data emerging for CXCR4 genotype in guiding therapy).
3) Patient preference
So what is the ‘best’ treatment?

Either approach can be very successful and if the disease progresses, the alternative approach can then be used.

You and your doctor (perhaps with help from a WM specialist) will make the best decisions for you, **BUT**

**Obviously Fixed duration is best!**

Only 6 months therapy, rapid, deep and prolonged responses, limited side effects, long treatment-free period.

“Set it and Forget it”
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TOO NUMEROUS TO PUT ON SLIDE

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THE CURE IS WITHIN
ABRAMSON CANCER CENTER
<table>
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<tr>
<th>Regimens</th>
<th>TTR</th>
<th>VGPR</th>
<th>PFS</th>
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<tbody>
<tr>
<td>CDR</td>
<td>8 weeks</td>
<td>20-30%</td>
<td>50% 3-4 years</td>
</tr>
<tr>
<td>BDR</td>
<td>4 weeks</td>
<td>30-40%</td>
<td>50% 5-6 years</td>
</tr>
<tr>
<td>Bendamustine-R</td>
<td>8 weeks</td>
<td>30-40%</td>
<td>50% 5-6 years</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>4 weeks</td>
<td>30-40%</td>
<td>50% 5-6 years</td>
</tr>
<tr>
<td>Ibrutinib-R</td>
<td>4 weeks</td>
<td>30-40%</td>
<td>UNK</td>
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<table>
<thead>
<tr>
<th>Ibrutinib</th>
<th>TTR</th>
<th>VGPR</th>
<th>PFS</th>
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</thead>
<tbody>
<tr>
<td>MYD88 only</td>
<td>4 weeks</td>
<td>40-50%</td>
<td>75% 5-6 years</td>
</tr>
<tr>
<td>CXCR4 mutated</td>
<td>8 weeks</td>
<td>10-20%</td>
<td>50% 4 years</td>
</tr>
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Ibrutinib works fast and induces long-lasting, deep responses
If you don't want....

- Steroids
- IgM flare
- Neuropathy
- Shingles prophylaxis
- Hours in an infusion room
- Secondary leukemia

And you are not afraid of...

- Taking 1 pill every day
- Small risk of atrial fibrillation
- Holding ibrutinib for a few days for procedures

Then, ibrutinib is for you!