Two Year Rituximab Maintenance after Chemo-immunotherapy Benefits and Risks

Lymphoma Support Group

June 6, 2023

Dr. Carolyn Faught

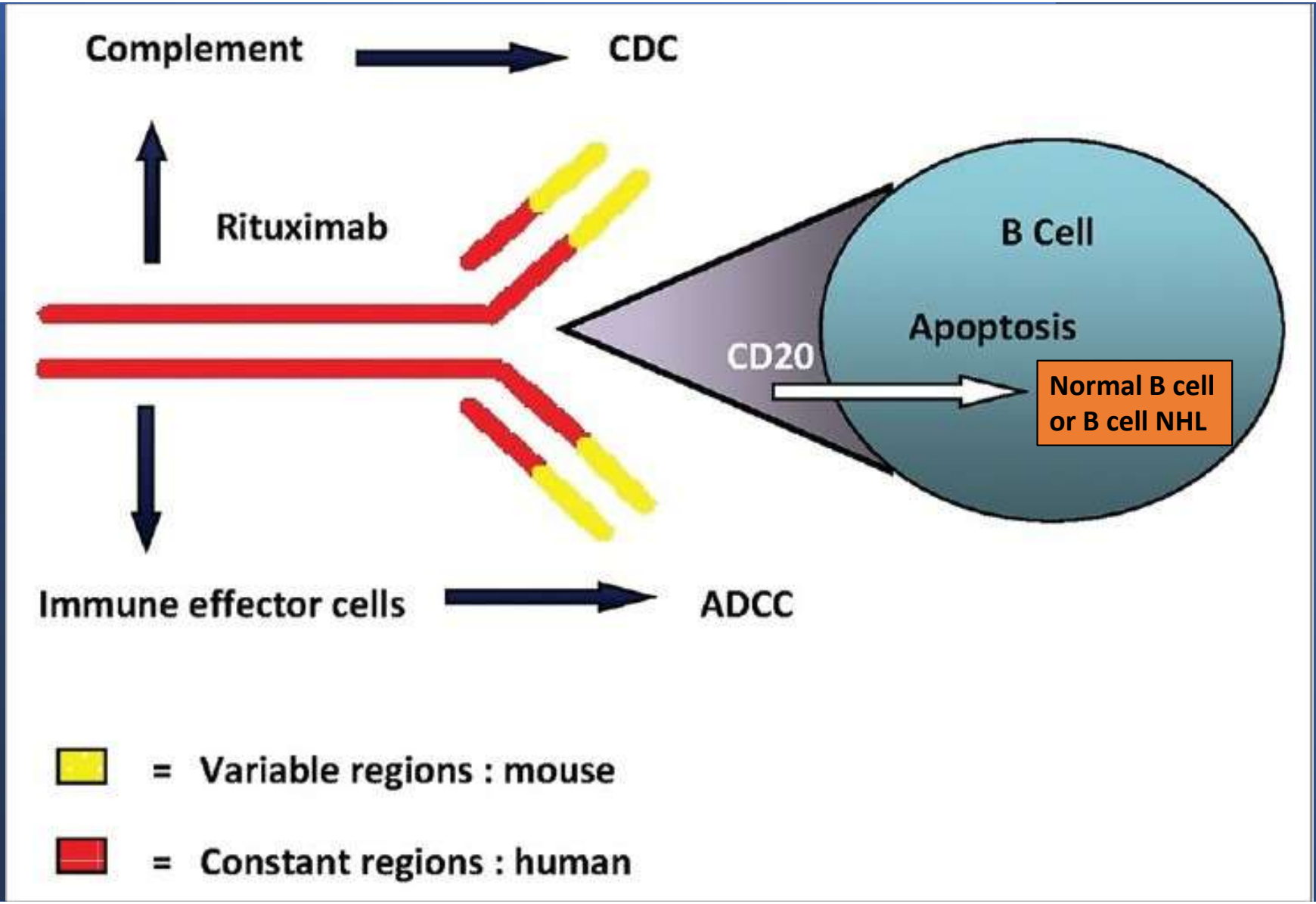
Objectives

1) Review literature supporting use of maintenance rituximab
2) Discuss potential side effects of prolonged rituximab use
3) How has COVID impacted decision making regarding maintenance
4) Case studies
5) Questions (at any time)

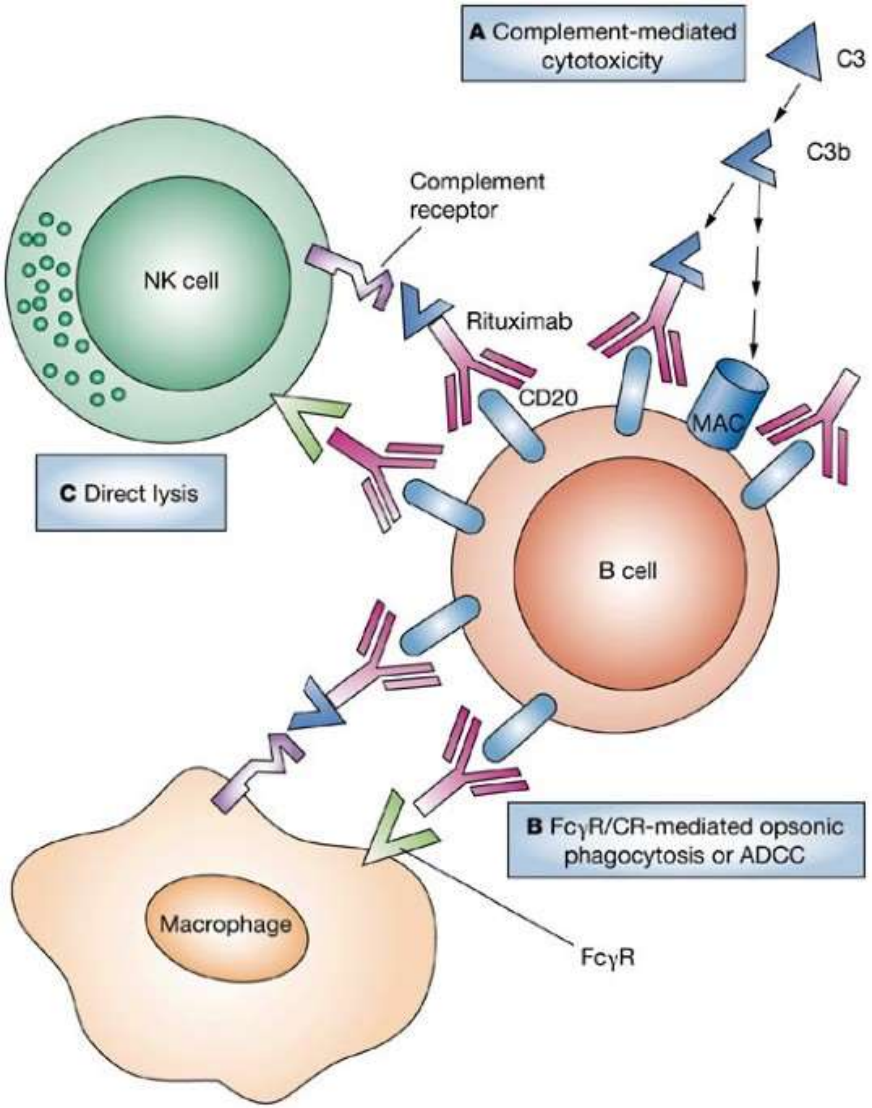
What exactly is maintenance rituximab?

...continued treatment beyond induction

Theoretical potential to clear minimal residual disease or convert PR (partial remission) into a CR (complete remission) with prolonged exposure


Complement
CDC
Rituximab
B Cell
Apoptosis
CD20
Normal B cell
or B cell NHL
Immune effector cells
ADCC
= Variable regions : mouse
= Constant regions : human

Mechanism of action of Rituximab



Facts about Rituximab Use

- Initially approved in 1998 for relapsed follicular lymphoma
- Used in all B cell Non-Hodgkin's lymphoma- usually with chemotherapy to increase response rates
- Used in non-malignant autoimmune conditions to suppress antibodies/B cells that cause disease (examples include rheumatoid arthritis, ITP, lupus, rare skin disorders)
- Not useful in T cell lymphomas
- Not useful in Hodgkin's lymphoma (exception being Nodular Lymphocyte predominant Hodgkin's)

Schedules for Maintenance Rituximab

- Many different schedules used: q 8 weeks, q 12 weeks, 4 consecutive weeks every 6 months for 2 years total
- Several RCTs using various chemotherapy regimens
  - In relapsing patients after chemo or R-chemo
  - In first line patients after chemo alone or rituximab alone
  - **In first line patients after R-chemo**

- Benefit most established for follicular lymphoma
- Benefit less clear after Bendamustine-rituximab chemotherapy

Canadian Approach

- Started using maintenance R in follicular lymphomas in 2006 based on Van Oers paper in ***relapsed setting***

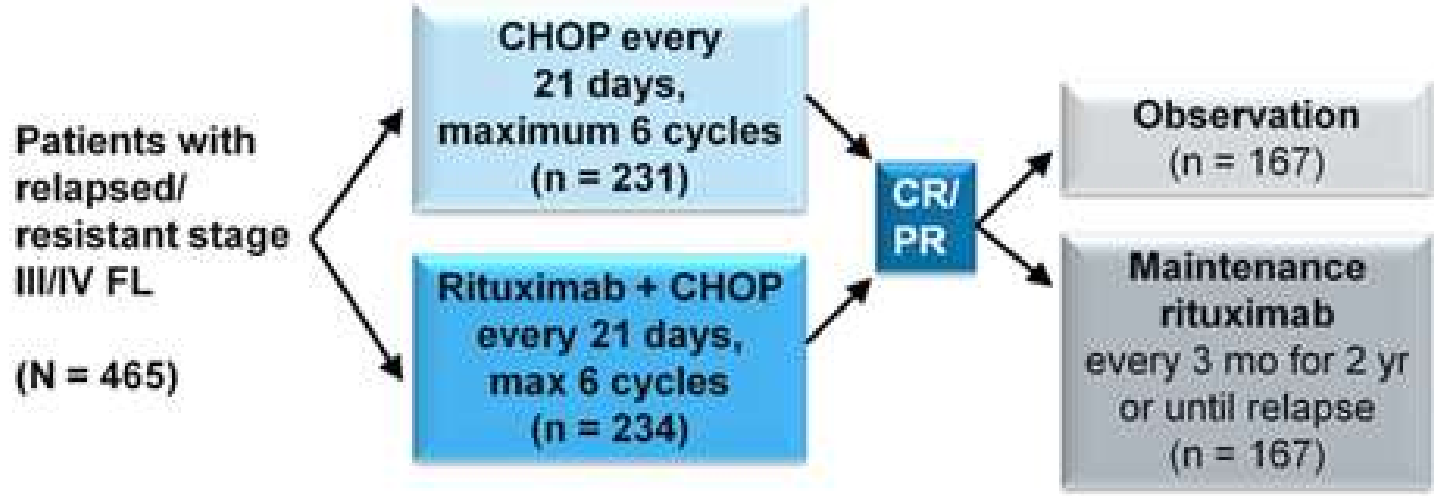
- Patients who are **treatment-naïve** receive R-chemotherapy and if in CR/PR go on to 2 year schedule of receiving IV rituximab every 12 weeks starting 12 weeks (up to 6 months) after induction chemotherapy

- Extrapolated its use to front line setting several years before many countries

Journal of Clinical Oncology 2006

Major benefit in PFS in both CHOP and RCHOP arms following maintenance R over observation

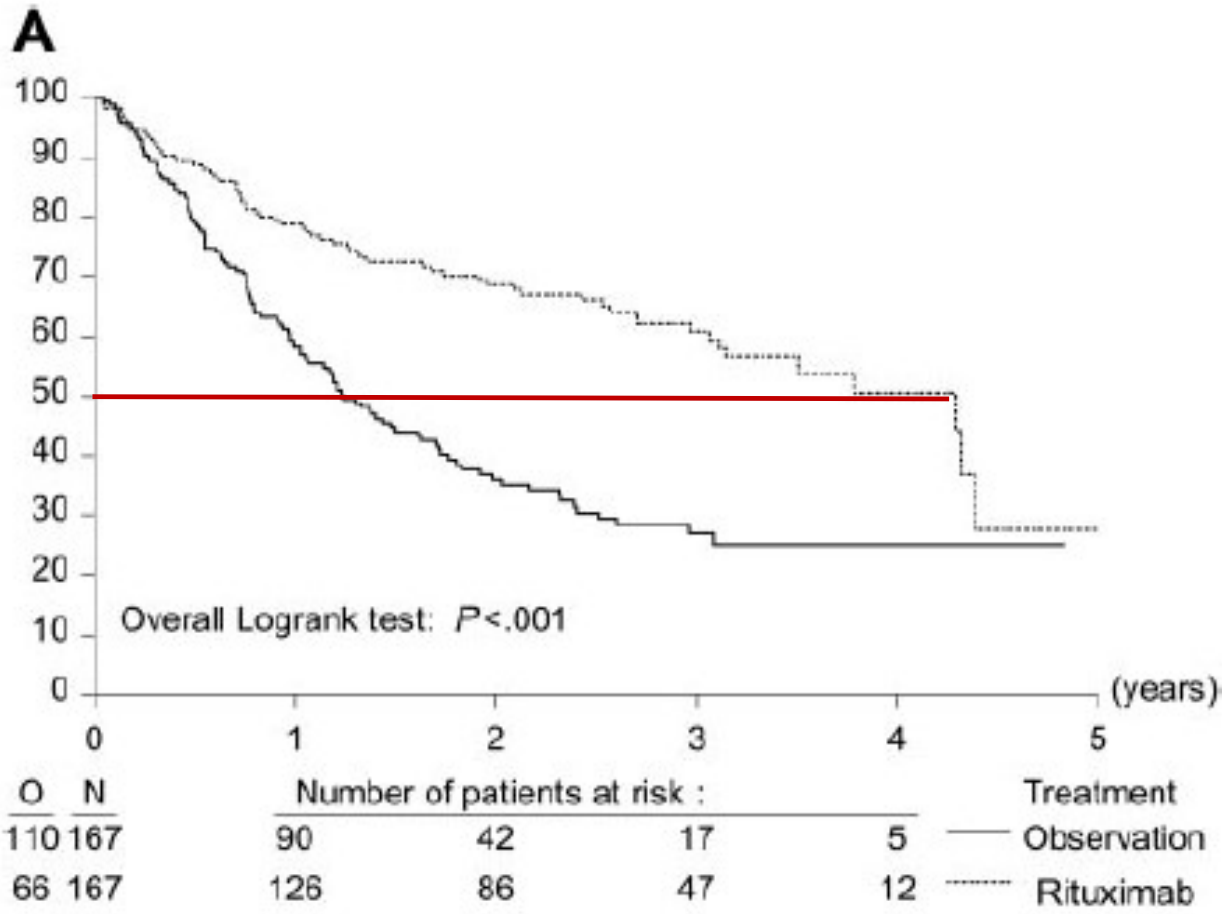
Phase 3 EORTC 20981 Trial
CHOP ± Rituximab ± Maintenance Rituximab



Van Oers MHJ, et al. *J Clin Oncol*. 2010;28:2853-2358. Reproduced with permission of the American Society of Clinical Oncology via Copyright Clearance Center.

Median PFS
51.5 months vs.
14.9 months
(P<0.001)

Grade ¾ infection rates 9.7% in maintenance arm vs 2.4% in observation (P= 0.01)



***Blood* November 2006**

Update 2010

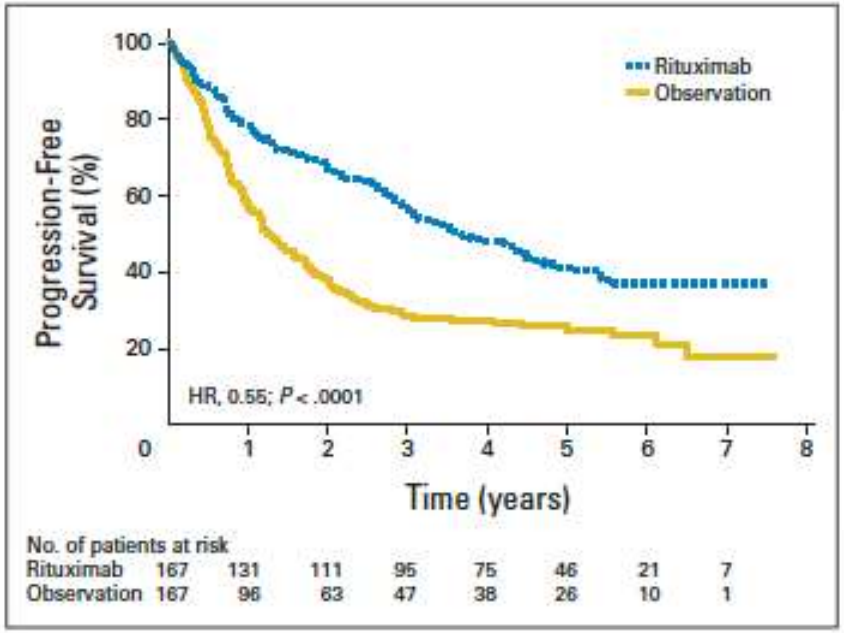


Fig 2. Effect of rituximab maintenance treatment on progression-free survival (PFS). Kaplan-Meier plot of PFS from second random assignment after rituximab maintenance therapy (n = 167) and observation (n = 167). Rituximab maintenance, median 3.7 years; observation, median 1.3 years. HR, hazard ratio.

VOLUME 28 · NUMBER 17 · JUNE 10 2010

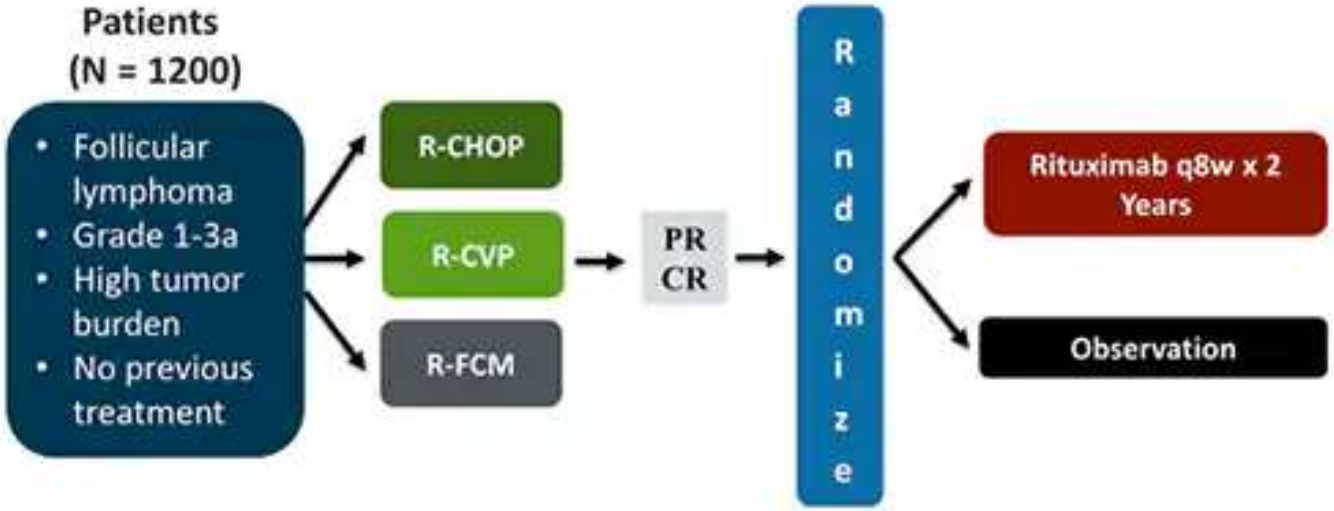
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Rituximab Maintenance Treatment of Relapsed/Resistant Follicular Non-Hodgkin's Lymphoma: Long-Term Outcome of the EORTC 20981 Phase III Randomized Intergroup Study

Marinus H.J. van Oers, Martine Van Glabbeke, Livia Giurgea, Richard Klasa, Robert E. Marcus, Max Wolf, Eva Kimby, Mars van t Veer, Andrej Vranovsky, Harald Holte, and Anton Hagenbeek

Blood 2011

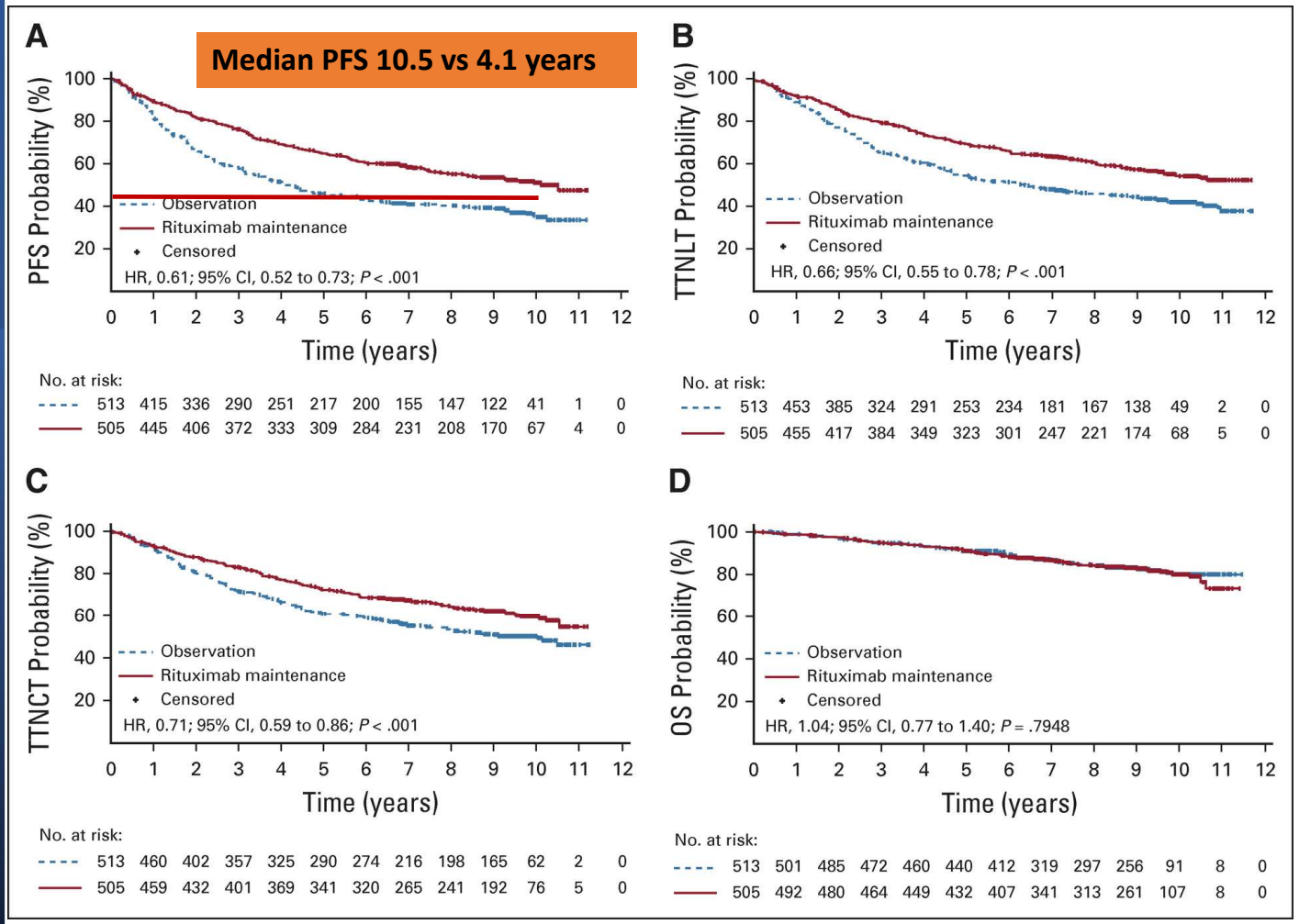
PRIMA Study: Rituximab Maintenance vs Observation



Outcomes, %	Rituximab Maintenance	Observation
Estimated 6-year PFS	59.2	42.7
Estimated 6-year OS	87.4	88.7

Salles, G, et al. *Lancet*. 2011;377:42-51.[28]
Salles GA, et al. *Blood*. 2013;122. Abstract 508.[29]

Long Term Follow Up of PRIMA Trial



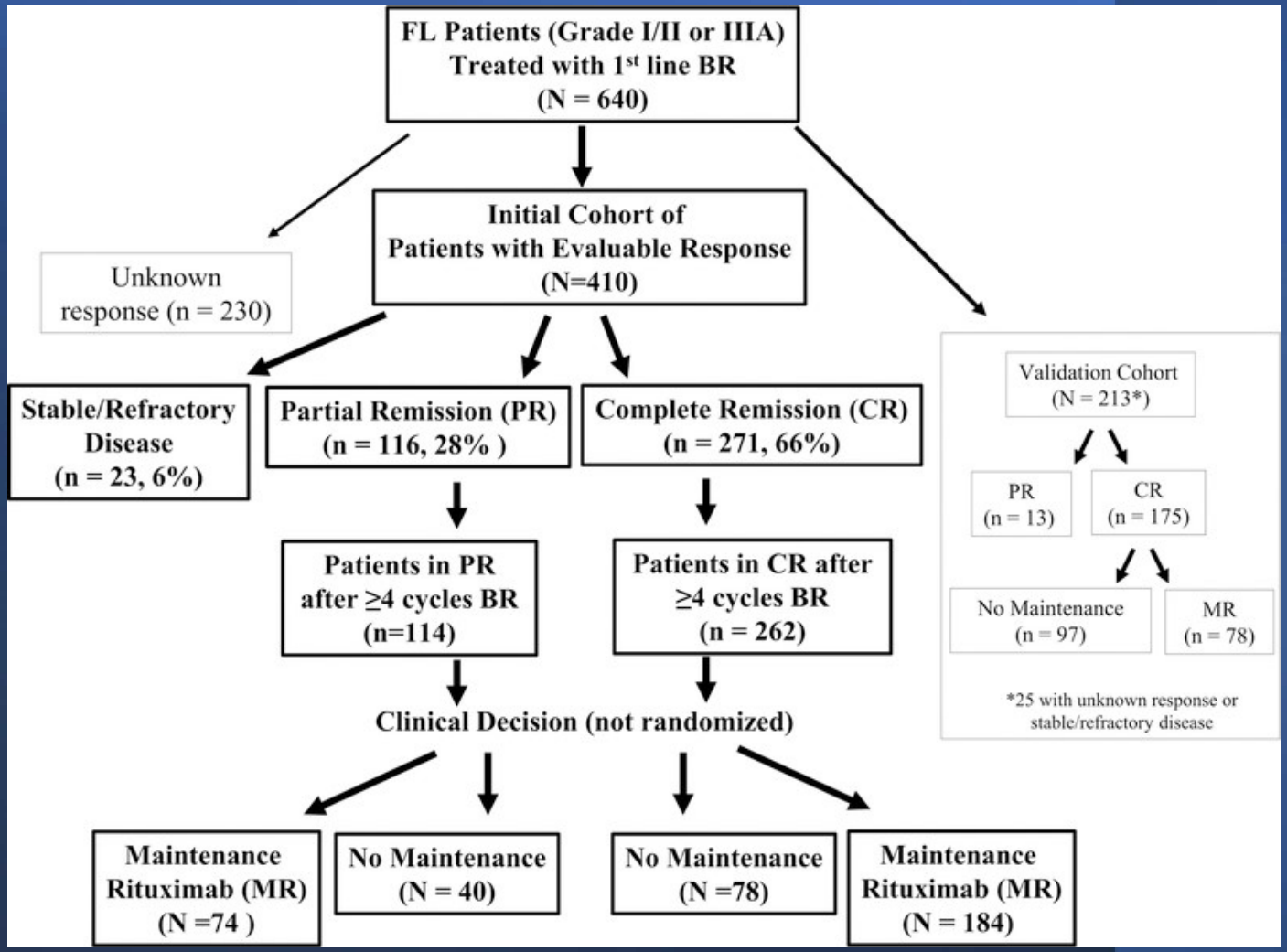
J Clin Oncology July 24, 2019

What is the evidence for maintenance following Bendamustine-rituximab induction?

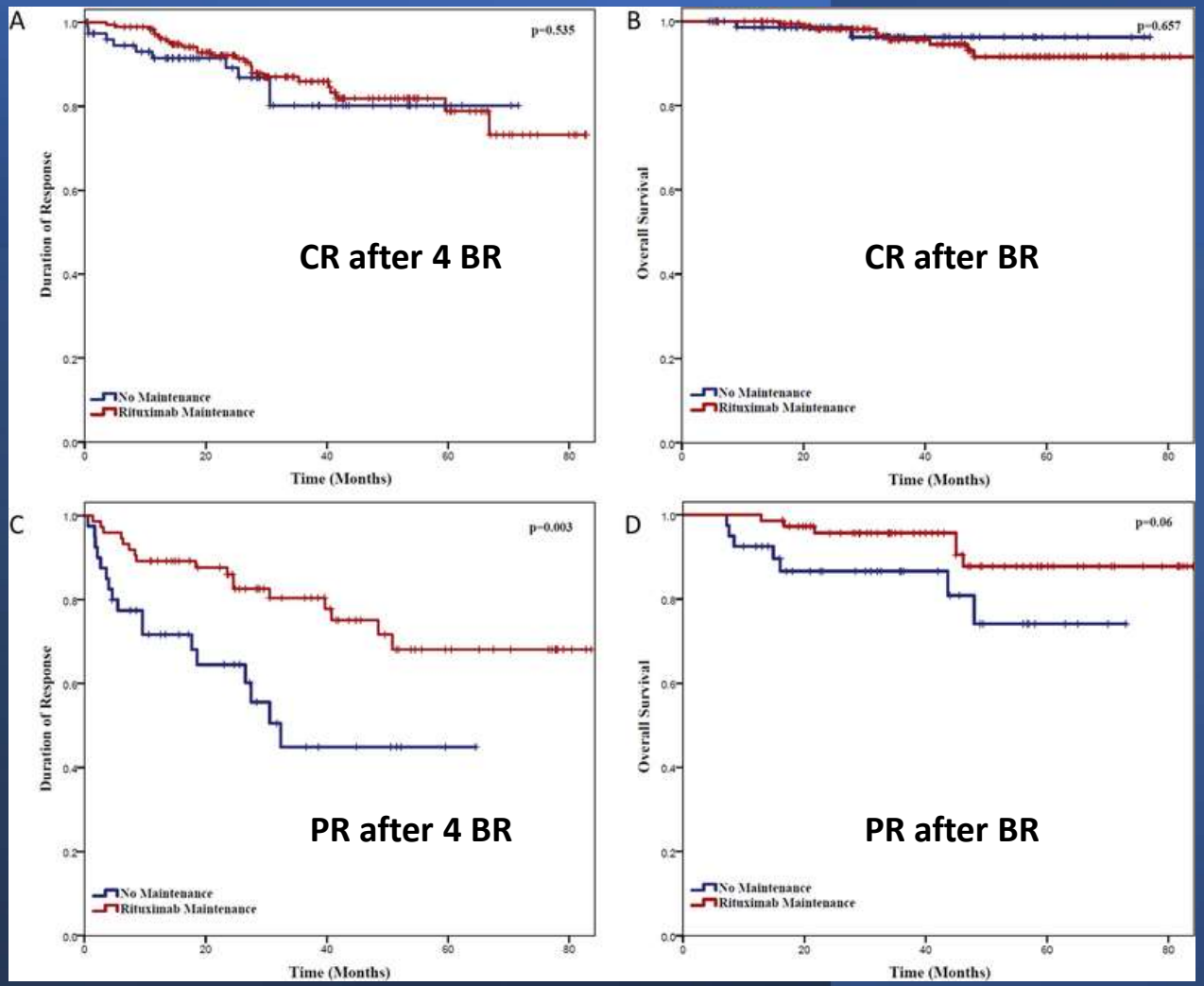
- RCT published in Lancet Oncology 2013 compared R-CHOP to R-Bendamustine in front-line setting (indolent B cell/mantle cell NHL)
- Trial showed superiority of R-Bendamustine
- This trial established Bendamustine-rituximab as gold standard
- In Canada we switched from RCVP/RCHOP to R-Bendamustine in June 2013
- **Trial did not include maintenance rituximab**

Large retrospective American study in *BJ Hem* Feb 2019
Retrospective look at 600+ patients with follicular NHL who received BR followed by maintenance or observation

Conclusion: Maintenance Rituximab only benefits those who are in PR after 4 cycles of BR, not those in CR.


FL Patients (Grade I/II or IIIA)
Treated with 1st line BR
(N = 640)
Unknown
response (n = 230)
Initial Cohort of
Patients with Evaluable Response
(N=410)
Validation Cohort
(N = 213*)
Stable/Refractory
Disease
(n = 23, 6%)
Partial Remission (PR)
(n = 116, 28%)
Complete Remission (CR)
(n = 271, 66%)
PR
(n = 13)
CR
(n = 175)
Patients in PR
after ≥4 cycles BR
(n=114)
Patients in CR after
≥4 cycles BR
(n = 262)
No Maintenance
(n = 97)
MR
(n = 78)
*25 with unknown response or
stable/refractory disease
Clinical Decision (not randomized)
Maintenance
Rituximab (MR)
(N =74)
No Maintenance
(N = 40)
No Maintenance
(N =78)
Maintenance
Rituximab (MR)
(N = 184)

Red = maintenance
Blue = observation



Evidence for Maintenance rituximab following Bendamustine-Rituximab

Benefit is less clear...

Is there evidence for other B cell NHLs?

- Mantle cell lymphoma (post ASCT and post BR without ASCT) - probably*
- Waldenstrom's macroglobulinemia - unlikely*
- Marginal zone lymphoma post BR - yes*

*Studies available upon request

2. Eligibility Criteria

Ontario

The patient must meet criteria a, b, c, and d:

* *a. Patient has follicular lymphoma or other indolent B-cell histology lymphoma (e.g., mantle cell lymphoma, marginal zone lymphoma, lymphoplasmacytoid lymphoma (Waldenstrom's macroglobulinemia), hairy cell leukemia, mucosa-associated lymphoid tissue (MALT) lymphoma but excluding diffuse small lymphocytic lymphoma/chronic lymphocytic leukemia)* ☑ Yes

* *b. Patient has received and responded to induction therapy with one of the following:*
  - ◉ *Rituximab in combination with chemotherapy*
  - ○ *Rituximab alone*
  - ○ *Chemotherapy alone*

* *c. Patient was rituximab naïve prior to induction therapy for indolent histology lymphoma* ☑ Yes

* *d. Maintenance rituximab will be initiated within 6 months of the last dose of induction therapy* ☑ Yes

Side Effects of Rituximab

- Infusion reactions - very common
- Any pulmonary toxicity - rare
- Severe mucocutaneous toxicity – extremely rare
- Serious/life-threatening cardiopulmonary events
- Reactivation of tuberculosis or hepatitis B
- PML (progressive multifocal leukoencephalopathy) - extremely rare but fatal
- Immunosuppression

Causes of Immunosuppression from Rituximab

NEUTROPENIA/WITH OR WITHOUT INFECTIONS

RECURRENT INFECTIONS
FROM SECONDARY HYPOGAMMAGLOBULINEMIA/B CELL DEPLETION

Neutropenia

- We usually consider neutrophils count < 1.0
- Incidence about 6%
- Can be late onset (3-4 weeks after last dose of rituximab)
- Mechanism unclear
- Can be managed with growth factor (grastofil, lapelga)
- Can lead to infections but not commonly
- If severe and recurrent may be a reason to stop rituximab
- Can last many months

Secondary Hypogammaglobulinemia

- Rituximab causes rapid drop in circulating CD20-expressing B cells which remain low or undetectable for 6-9 months before returning to pre-treatment levels
- Incidence of hypogammaglobulinemia (low IgG) 39% in one US review of patients with NHL treated between 1998-2009. Worse with maintenance
- 6.6% required IV IgG for recurrent sinopulmonary infections
- More written about IgG depletion in autoimmune conditions like RA

Brief report

Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment

Olav Erich Yri,[1] Dag Torfoss,[1] Olav Hungnes,[2] Anne Tierens,[3] Kristian Waalen,[2] Tone Nordøy,[4] Susanne Dudman,[2] Anette Kilander,[2] Karin Fahl Wader,[5] Bjørn Østenstad,[1] Roald Ekanger,[6] Peter Meyer,[7] and Arne Kolstad[1]

- **Blood, 22 December 2011**

What about response to vaccine?

62 patients with NHL treated with rituximab within the last 6 months

Excluded patients who had previous exposure to H1N1

82% of controls responded none of 62 patients had adequate response to swine flu vaccine

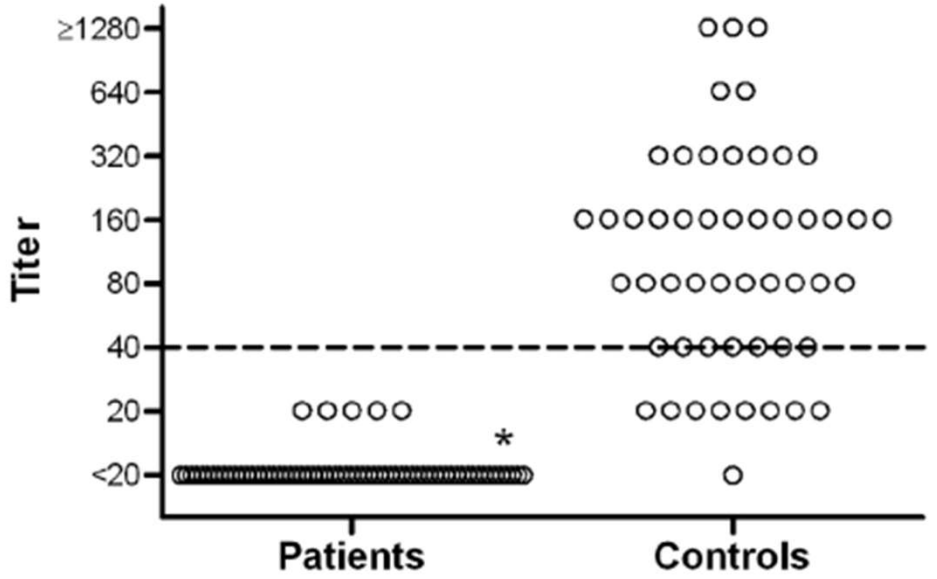


Figure 1. Postvaccination antibody titers in patients and controls. Titers are given as the reciprocal value of the highest dilution inhibiting the hemagglutination reaction. The dotted line indicates the protective antibody level of 40. *A total of 62 patients had an undetectable postvaccination titer.

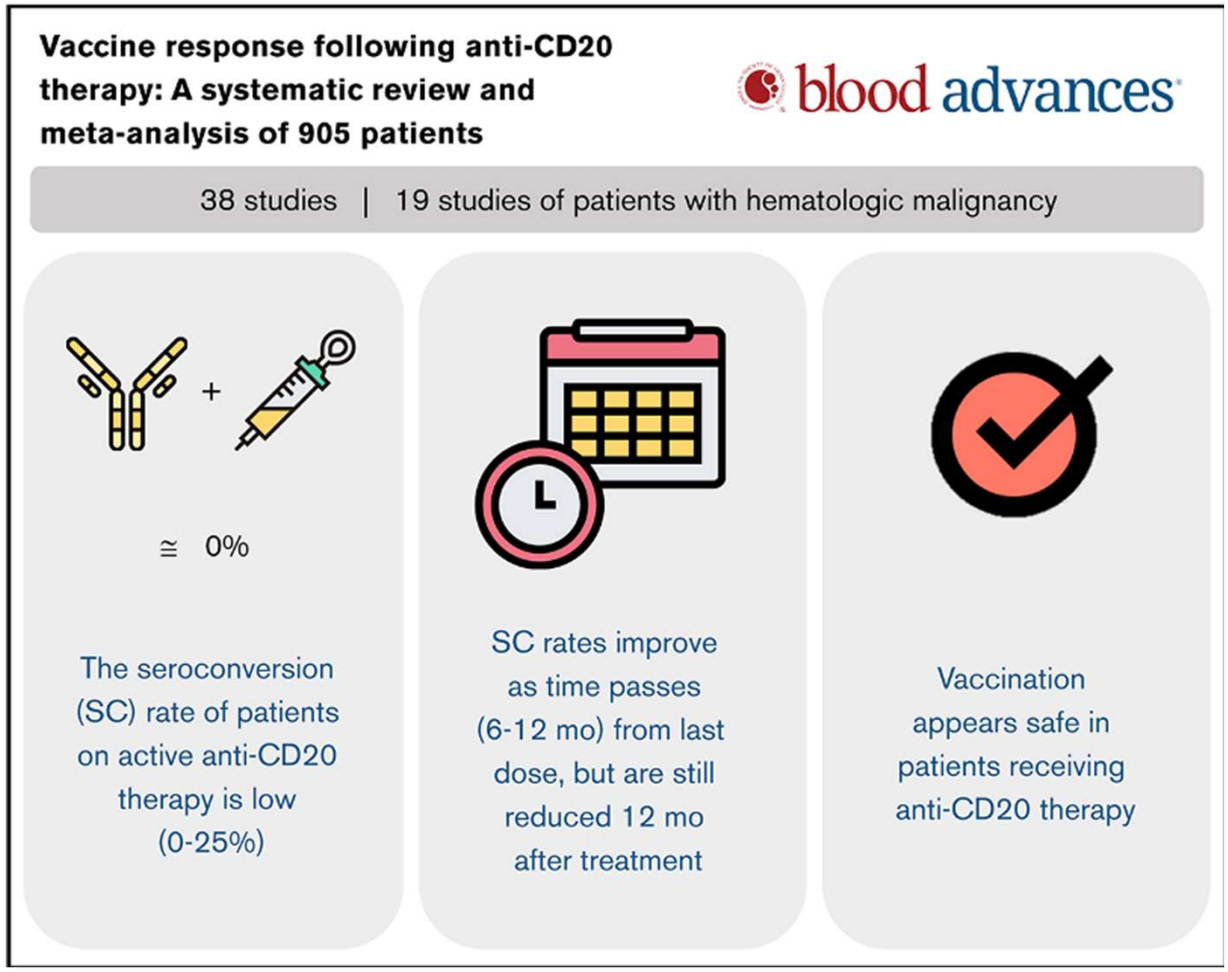
Vaccine response following anti-CD20 therapy; systematic review and meta-analysis of 905 patients

Blood Advances 22 June 2021

Abi Vijenthira from PMH

VACCINES

Influenza (flu vaccine)
Diptheria
H. influenza
Polio
Pneumococcal
Hepatits A
Hepatitis B



Rituximab and Vaccinations

- Ideally vaccinate 1-2 weeks before starting rituximab

- Patients with blood cancers and other cancers not on rituximab respond to vaccine but lower than normal host

- Don't forget about the T cells...
- **Studies have shown that rituximab does not impair the cellular response to vaccines (T cell response)**

COVID-19 pandemic

How has this impacted patients on rituximab?

Response to Covid-19 vaccines in patients receiving Rituximab

- Very low response to COVID-19 vaccines
- < 10 %
- Effect last up to 9-12 months since last dose
- After 12 months still not optimal compared to controls

- More recent studies have shown that there is still a robust CD8 T cell response to vaccine – likely helps mitigate the severity of Covid infection

Covid-19 Pandemic

- Like everyone we didn't know the severity of Covid initially or the true impact on our patients
- Studies started being published showing mortality rates among the highest in hematology patients (~ 30%)
- **People on anti-CD20 therapy in highest risk category**
- By summer of 2020 due to concerns about hospitals in Ontario being overwhelmed cancer centers started making triage lists in order of priority for treatment
- Those qualifying or already on maintenance rituximab considered "low hanging fruit"- deemed not essential

Post-Covid Pandemic Thoughts

- Does everyone who qualifies need/stand to benefit from maintenance rituximab?
- Speak to your physician about the risks/benefits
- Your decision may depend on your age, comorbidities, concerns about the prolonged immunosuppression,etc.

QUESTIONS

Case #1

- 68 year-old female
- Stage IIIA follicular NHL 2006
- Received RCHOP followed by 2 years of maintenance rituximab
- **First patient of mine to receive maintenance rituximab starting in 2006**
- In complete remission since finishing RCHOP based on CT criteria
- No recurrence in 17 years!

Case # 2

- 68 year-old female with Follicular lymphoma grade 3A, stage IIIA
- Treatment: RCHOP followed by maintenance rituximab 2012-2014
- Relapsed disease, follicular lymphoma, grade 1-2 2016.
- R-Bendaumustine 2016 followed by maintenance rituximab. 5/8 rituximab completed but discontinued due to recurrent sinus infections from secondary hypogammaglobulinemia.
- IgG 2.2 g/L --> Weekly Cuvitru SC (IgG) started
- Covid vaccines all on schedule
- Covid twice in 2022

Case #3

- 88 year-old female presented with severe hypertension. No previous health condition. Found to have renal artery stenosis and large retroperitoneal mass causing right hydronephrosis (enlarged kidney)
- Core biopsy of mass shows follicular lymphoma
- She is reluctant to have any treatment.
- Creatinine elevated, on 3 BP pills with ongoing hypertension
- Agrees to reduced dose Bendamustine/rituximab (50% benda) for 6 cycles
- Interim and final CT scan shows shrinkage of mass and improvement in hydronephrosis
- Should she receive maintenance rituximab?

Case

- 57 year old male with follicular lymphoma, mesenteric mass, slowly growing
- Stage IA, FLIPI 0, initial diagnosis 2017; watch and wait x 3 years
- Received bendamustine/rituximab x 6 months completed in June 2020.
- Achieved CR
- Started maintenance rituximab
- No issues – had 3 Covid vaccines all while receiving rituximab
- Cycle #7 January 2022
- Presented to ER in Cornwall with bad Covid pneumonia 4 weeks later
- Unfortunately died in our ICU a 2 weeks later