Monoclonal antibody ; Rituximab

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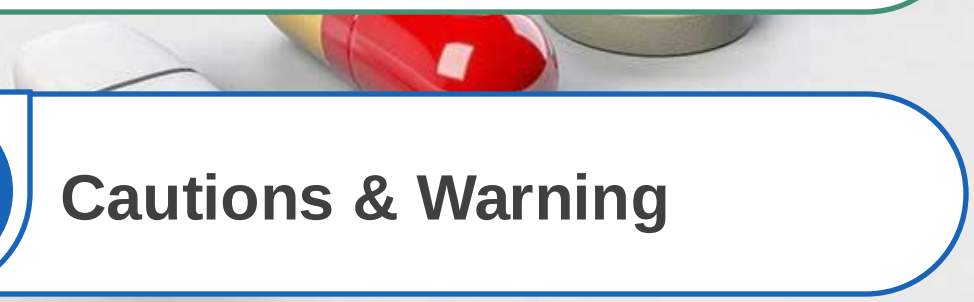

1-MOA

Rituximab is an anti **CD20** chimeric antibody

- CD20 is a surface **transmembrane protein marker** expressed on **B cells** during differentiation from the pre-B cell until the plasma cell stage.
- CD20 is believed to function as a **calcium channel** and play **a role in the maturation and activation of B cells**

❑ Once rituximab is bound to CD20 positive cells, **cell death** is induced by various mechanisms, including :

- antibody-dependent cell-mediated cytotoxicity (ADCC),
- complement-mediated-cytotoxicity(CDC)
- antibody-dependent phagocytosis (ADP),
- direct effects of binding of rituximab to CD20.

Rituximab combination

Combination of rituximab and hyaluronidase

Rituximab-hyaluronidase human is used in **subcutaneous form**.

i.e. Hyaluronidase causes a reversible increase in permeability of subcutaneous tissue by causing depolymerization of hyaluronan,

leading to an **increase in the absorption rate of rituximab**.

2-Therapeutic applications

Pediatrics

1- Leukemia, acute B-cell; CD20+; advanced stage, previously untreated:

❑ **Infants ≥6 months, Children, and Adolescents:**

- IV infusion: **375 mg/m²/dose** in combination with systemic (LMB) chemotherapy regimen

2- Acute lymphoblastic leukemia, mature B-cell, CD 20+ (B-ALL); relapsed/refractory:

❑ **≥5 years and Adolescents:**

- IV infusion: **375 mg/m²** administered **on days 1 and 3** of **courses 1 & 2**

- **On day 1 only** of **course 3** ; used in combination with **ifosfamide**, **carboplatin**, and **etoposide** (ICE)

Lymphome Malin B (LMB)

LMB 2001 was a FAB (**French-American-British**) /LMB 96-based protocol.

❑ Treatment was based on **St Jude's/Murphy's stage** (Staging system for childhood NHL)

All patients received a prephase of

low-dose cyclophosphamide, **vincristine**, and **prednisone** (COP).

Administer :

- **2 doses** during each **induction course** (day 1 and day 2),
- **1 dose** on **day 1** of each of the **2 consolidation cycles** (6 doses total)

2- Therapeutic applications

Pediatrics

3- Non-Hodgkin lymphoma; CD20+, diffuse large B-cell, Burkitt lymphoma, Burkitt-like lymphoma; previously untreated, advanced stage

Infants ≥6 months, Children, and Adolescents:

- IV infusion: **375 mg/m^2/dose** in combination with systemic (LMB) chemotherapy regimen;
- Administer:

✓ **2 doses** during each **induction course** (**day –2 and day 1),**

✓ **1 dose** on **day 1** of each of the **2 consolidation** cycles (6 doses total).

Ataxia patients LMB protocol modifications

Group A

Completely resected stage I, & completely resected abdominal stage II

2 courses R-COPAD

D0	D1	D2	D3	D4	D5	D6
Rituximab	Pred CTX VCR Adria	Pred CTX	Pred CTX	Pred	Pred	VCR

Rituximab: 375mg/m^2

Prednisone (Pred): 60 mg/m^2/day (divided into bid doses) orally (or IV) on days 1-5 inclusive then reduced to zero over 3days.

Cyclophosphamide(CTX): 125 mg/m^2 12 hourly as 15-minute infusion on D1-3 inclusive (250 mg/ m^2 /day) The first dose should be given on day 1 prior to the start of the doxorubicin infusion. Hydration should be maintained at a rate of 3000 mls/m^2/day (125 mls/m^2/hr). Continue hydration until 12 hours after the last dose of cyclophosphamide.

Adriamycin(Adria): 30mg/m^2 as 6-hour infusion, after the first dose of Cyclophosphamide.

Vincristine (VCR): 1mg/m^2 IV bolus D1 and D6. (Maximum single dose 2.0 mg).

Notes:

*CBC, serum electrolytes, BUN, creatinine, bilirubin, SGOT/SGPT before each cycle.

*CR evaluation after COPAD (II) including CSF exam, BM exam and imaging studies of 1ry tumor site should be done after count recovery.

*Re-evaluation will be done by conventional methods [Chest X-ray, Abd US], serum LDH after 2 courses of chemotherapy.

*Avoid ionizing radiation [CT scan, PET CT]

*If patients are not in remission after two courses of COPAD (as confirmed by biopsy), they will then advance to induction in Group C (2^{nd} COPADM8).

Induction
R-COPADM3-I > R-COPADM3–II

D0	D1	D2	D3	D4	D5	D6
Rituximab	Pred HDMTX VCR	Pred CTX Adria IT	Pred CTX	Pred CTX IT*	Pred	IT

Rituximab: 375mg/m^2
Prednisone (Pred): 60 mg/m2/day (divided into BID doses) orally on days 1 -5 inclusive then reduced to zero over 3 days.
Cyclophosphamide(CTX): 125 mg/m^2 12 hourly as 15-minute infusion on D2-4 inclusive (250 mg/ m^2 /day) The first dose should be given on day 1 prior to the start of the doxorubicin infusion. Hydration should be maintained at a rate of 3000 mls/m^2/day (125 mls/m^2/hr). Continue hydration until 12 hours after the last dose of cyclophosphamide.
Adriamycin (Adria): 30mg/m^2 as 6-hour infusion, after the first dose of Cyclophosphamide.
Vincristine (VCR): 1mg/m^2 IV bolus D1 (Maximum single dose 2.0 mg).
High Dose Methotrexate (HDMTX): 1g/m^2 iv infusion over 4 hours with rescue Ca leucovorin according to protocol.
IT (HC + MTX) *: Additional Intrathecal on D4 for patients with **CNS disease (Group C).**
Calcium Leucovorin: 15 mg/m^2 orally every 6 hours for a total of 12 doses (or as required depending on methotrexate levels).

Consolidation

CYMI CYMII

D0	D1	D2	D3	D4	D5	D6	D7
Rituximab	HDMTX	Ara-C IT_1	Ara-C	Ara-C IT*	Ara-C	Ara-C	IT_2

Rituximab: 375mg/m^2

High Dose Methotrexate (HDMTX): 1g/m^2 1g/m^2 iv infusion over 4 hours with rescue Ca leucovorin according to protocol .

Calcium Leucovorin: 15 mg/m_2 orally every 6 hours for a total of 12 doses (or as required depending on methotrexate levels).

Cytrabine (Ara-C): 100 mg/m_2 in 1000 mls/m_2 dextrose saline as infusion over 24 hours. Repeat daily from Day 2-6 inclusive.

IT_1 (HC + MTX): Each dose adjusted.

IT_2 (HC + Ara-C): Each dose adjusted.

IT (HC + MTX) *: Additional Intrathecal on D4 for patients with **CNS disease (Group C).**

Further reduction of cytotoxic chemotherapy should be suggested guided by the patient general

Notes:

*The interval between 1st and 2nd consolidation phase should be reduced to minimum. Each course should be given upon hematological recovery (ANC=1000, Pt=100,000).

*CBC, Lytes, BUN, Creatinine, Bilirubin, SGOT/SGPT, Uric acid and Phosphorus should be done twice weekly during chemotherapy.

*CR evaluation after CYM I; including CSF exam, BM exam, imaging studies of 1ry tumor site should be done after count recovery.

*Re-evaluation will be done by conventional methods [Chest X-ray, Abd US], serum LDH after 2 courses of chemotherapy.

*Avoid ionizing radiation [CT scan, PET- CT].

2-Therapeutic applications

P e d i a t r i c s

4- Non-Hodgkin lymphoma B-cell, CD 20+; relapsed and refractory:

Children ≥11 years and Adolescents:

- IV infusion: **375 mg/m²** administered **on days 1 and 3** of **courses 1 & 2**
- **On day 1 only** of **course 3** ; used in combination with **ifosfamide**, **carboplatin**, and **etoposide** (ICE)

Clinical considerations !!!!

For oncology uses, a **uricostatic agent** (eg, allopurinol) and **aggressive hydration** are recommended for patients at risk for tumor lysis syndrome

Preparation & Administration

3- Preparation

- Rituximab should be diluted in an infusion bag of either 0.9% sodium chloride or 5% dextrose in water.
- No other drugs should be mixed with it, and patients should be closely monitored for infusion reactions.

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4- Administration guidelines

- Rituximab and its biosimilars are approved for use by intravenous infusion.
- They should not be administered as IV bolus or push.
- Patients should be given **acetaminophen** and **antihistamine** before each infusion.

5-Emetic potential

- ❑ Pediatrics and Adults: Minimal (<10%)
- ❑ Dose-adjusted EPOCH and rituximab (DA-EPOCH-R), a **treatment regimen** used for subsets of patients with aggressive non-Hodgkin B-cell lymphoma, is considered **highly emetogenic** as it contains the combination of doxorubicin and cyclophosphamide.
- ❑ The DA-EPOCH multiday regimen includes :
- ❑ **etoposide**, **vincristine**, **doxorubicin :** infused continuously over days 1 to 4,
  - cyclophosphamide given on day 5,
  - 60 mg/m^2 of prednisone taken by mouth twice daily on days 1 to 5

6-Management of adverse effects

Risk points	Managing toxicity
Bowel obstruction/perforation : ▪ Association between **depletion of B-cells** and **severe colitis**.	• Tell your healthcare provider right away if you have any stomach-area pain during treatment with Rituxan
Cytopenia : • Rituximab is associated with lymphopenia, leukopenia, neutropenia, thrombocytopenia, and anemia; • Duration of cytopenias may be prolonged and may extend months beyond treatment.	✓ Monitor **CBC**
Renal toxicity: May cause fatal renal toxicity in patients with non-Hodgkin lymphomas (NHL). & Renal toxicity also occurred due to tumor lysis syndrome.	➢ Monitor **kidney functions**

Risk points	Managing toxicity
Tumor lysis syndrome : ▪ Leading to acute renal failure requiring dialysis (sometimes fatal) may occur within 12 to 24 hours following the first dose when used as a single agent in the treatment of NHL. ▪ Hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia may occur.	❑ Administer prophylaxis : **antihyperuricemic therapy** and **aggressive hydration** in patients at high risk ❑ Correct electrolyte abnormalities and administer supportive care as indicated.
Serious Infusion-related reactions Reactions may include : angioedema, bronchospasm, cough, hypotension, hypoxia, throat irritation, urticaria, and in more severe cases, acute respiratory distress syndrome, pulmonary infiltrates, acute myocardial infarction, ventricular fibrillation, and **cardiogenic shock**	**Management of Rituximab anaphylaxis :** Hypersensitivity reactions to first-dose rituximab treatment can be reduced by **priming intravenous lines with Standardized premedications**, including : ➢ **acetaminophen,** ➢ **diphenhydramine** ➢ **dexamethasone**

Risk points	Managing toxicity
Hypogammaglobulinemia (LOW AB) and Infection ; (dose related) Serious, including fatal, bacterial, fungal, and new or reactivated viral **infections** can occur during and following the completion of rituximab-based therapy Infections have been reported in some patients with prolonged **hypogammaglobulinemia**. New or reactivated viral infections have included **CMV viremia**, **herpes simplex infection**, **parvovirus B19 seroconversion**, **varicella zoster infection**, West Nile virus, and **hepatitis C** and B.	❑ **Management :** **Trimethoprim-sulfamethoxazole prophylaxis** prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis

7-Drug interaction :

Amphotercin B & Cisplatin : both increase nephrotoxicity and/or ototoxicity (category c)

8- WHAT ARE WARNINGS AND PRECAUTIONS FOR RITUXIMAB?

1- Mucocutaneous reactions (severe):

Severe, including fatal, mucocutaneous reactions reported including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis

2- Progressive multifocal leukoencephalopathy:

•John Cunningham virus infection resulting in progressive multifocal leukoencephalopathy and death has been reported in patients treated with rituximab

3- Reactivation of hepatitis B:

•Screen all patients for HBV infection before initiating drug by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc)

•Consult with hepatitis experts regarding monitoring and use of HBV antiviral therapy when screening identifies patients at risk of HBV reactivation due to evidence of prior HBV infection

Difference between Rituximab & Brentuximab ?

- Brentuximab vedotin is an **immunotoxin targeting CD30-expressing cells**, including those in Hodgkin lymphoma
- It is approved for treatment of relapse/refractory Hodgkin lymphoma
- First line treatment of Hodgkin lymphoma.
- Compared to conventional chemotherapy, Both rituximab and brentuximab vedotin are better tolerated with less toxicity.

Adverse effects :

Immediate effects after having brentuximab (infusion related)

You might have a **rash**, **shortness of breath**, **difficulty breathing**, a **cough**, a **tight chest**, **fever**, **back pain**, **chills, headache**, feeling sick or being sick. These can happen within a few minutes or up to several hours after having brentuximab. This can be life threatening.

Thank you !

Any questions ?

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