# Comparative Outcomes Following CP-R, CVP-R and CHOP-R in Patients with Waldenstrom's Macroglobulinemia

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# Introduction

- Randomized studies incorporating Rituximab in indolent lymphomas showed improved overall response, complete response, time to progression and overall survival with CHOP and CVP;
- In WM patients, the German Low Grade Study Group showed improved overall response, complete responses, time to progression were significantly improved in patients receiving CHOP+Rituximab versus CHOP;
- Similar results to those attained with CHOP-R however were seen in a recent study by Dimopoulos et al in patients receiving R-CD;
- These studies raise the question whether Doxorubucin (“H” in CHOP) and Vincristine (“O” in CHOP or “V” in CVP) are necessary in treating indolent lymphomas like WM given their toxicities.

# Chemotherapy related Toxicities

- Doxorubicin

  Can lead to heart failure, moderate to severe nausea/vomiting, loss of hair, skin irritation at site of injection, decrease in blood counts, susceptibility to infections.

- Vincristine

  Significant neuropathy, significant constipation, decrease in blood counts loss of hair.

# Study Design

- Comparison of activity and toxicity in WM patients who received cyclophosphamide based therapy with rituximab.

**•CHOP-R ( n= 23)**

**•CVP-R ( n= 16)**

**•CP-R (n= 19)**

Ioakimidis et al, Clin Lymph Myeloma 2009.

# Study Comparison of CHOP-R , CVP-R, CP-R

- Response rates
  -- overall, major, and complete response rates
- Progression free survival (PFS)
- Improvements in hematological function
- Treatment related adverse events
  -- occurrence of febrile neutropenia, hospitalizations, neuropathy, occurrence of rituximab -related “IgM flare”, and need for plasmapheresis as a result of “IgM flare”

# Therapy

**CHOP-R**

-- Intravenous (IV) Cyclophosphamide ( 750 mg/$m^2$)
-- Intravenous (IV) Doxorubicin ( 50 mg/$m^2$)
-- Intravenous (IV) Vincristine ( 1.4 mg/$m^2$; max 2 mg)
-- Intravenous (IV) Rituximab on day 1 (375 mg/$m^2$)
-- Oral Prednisone (100mg)  Days 1-5

**CVP-R**

-- Intravenous (IV) Cyclophosphamide ( 750- 1000 mg/m2)
-- Intravenous (IV) Vincristine ( 1.4 mg/m2; max 2 mg)
-- Intravenous (IV) Rituximab on day 1 (375 mg/m2)
-- Oral Prednisone (100mg)  Days 1-5

**CP-R**

-- Intravenous (IV) Cyclophosphamide (1000 mg/m2)
-- Intravenous (IV) Rituximab on day 1 (375 mg/m2)
-- Oral Prednisone (100mg)  Days 1-5

# Baseline Characteristics

| | CHOP-R | CVP-R | CP-R |
|---|---|---|---|
| **(N)** | **23** | **16** | **19** |
| **Median Age** | **54 Years** ( 42-74) | **60 Years** ( 32-81) | **65 Years** ( 42-74) |
| **Median Previous Therapies** | **0** (0-2) | **1** (0-3) | **0** (0-2) |
| **No Previous Therapy** | **57%** | **29%** | **63%** |

p= not significant for all comparisons.

Ioakimidis et al, Clin Lymph Myeloma 2009.

# Baseline Characteristics

| | CHOP-R | CVP-R | CP-R |
|---|---|---|---|
| **Median Bone Marrow Involvement** | 50% | 50% | 45% |
| **Serum IgM (mg/dL)** | 5,190 | 2,515[a] | 2,665[b] |
| **Hematocrit (%)** | 31.3 | 30.2 | 33.4 |
| **Platelet count (x $10^9$/L)** | 242 | 169 | 270 |
| **$B_2$ microglobulin (mg/L)** | 3.6 | 3.3 | 2.4 |
| **Adenopathy and/or Splenomegaly** | 34.7% | 25% | 31.6% |
| **Cycles of therapy** | 6 | 6 | 6 |

p= Not significant except (a) = 0.015( CHOP-R vs. CVP-R) and (b)= 0.014 ( CHOP-R vs. CP-R)

# Response Rates

- **Complete response (CR)** : resolution of all symptoms, normalization of serum IgM levels and disappearance of IgM, and resolution of any adenopathy or spenomegaly.

- **Near-CR (nCR)** : fulfilling all CR criteria but presence of positive immunofixation

- **Very good partial response (VGPR)** : ≥ 90% reduction in serum IgM

- **Partial Response (PR)** : 50-89% reduction in serum IgM

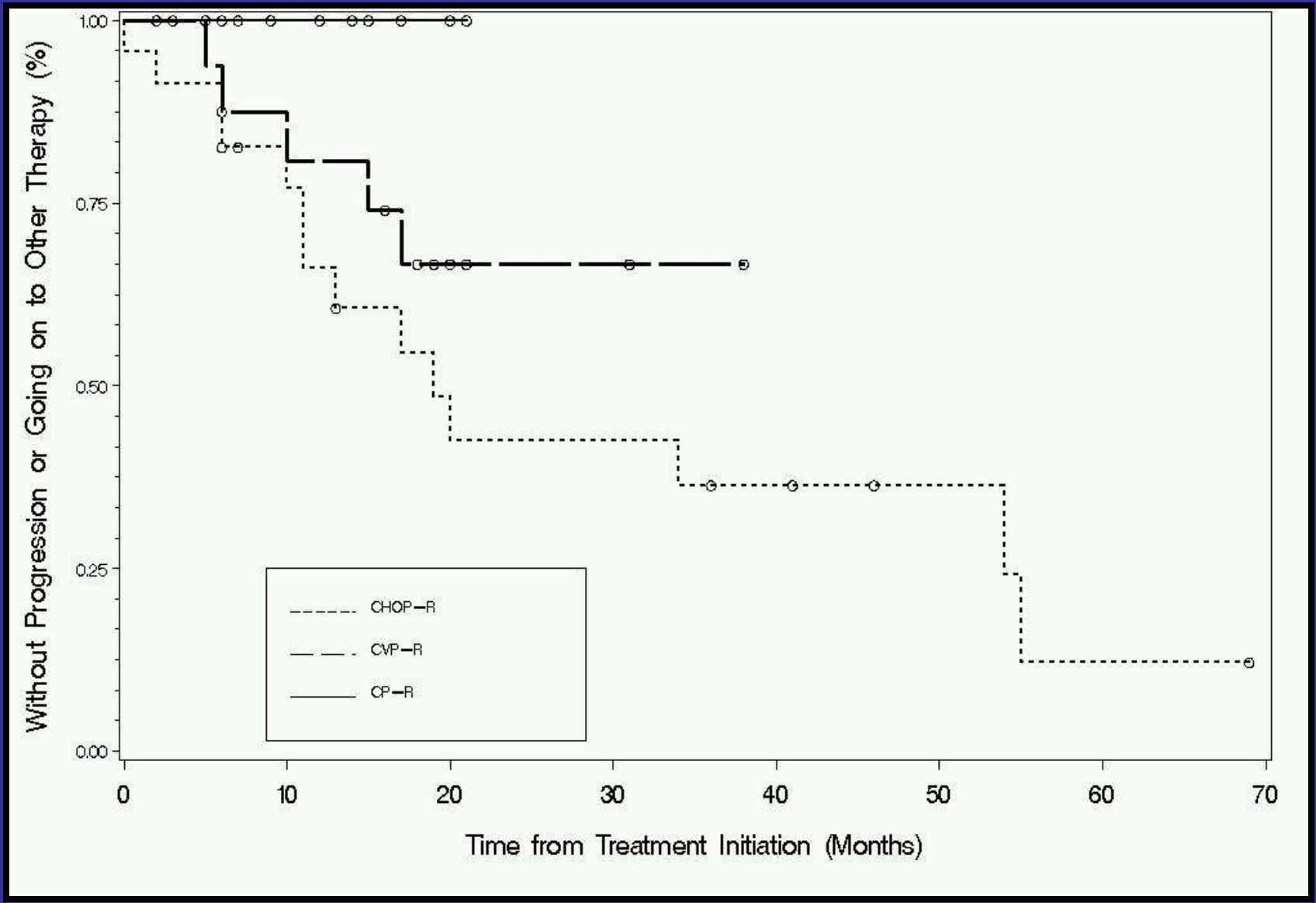
- **Minor Response (MR)** : 25-49% reduction in serum IgM

- **Progressive disease (PD)** : > 25% increase in serum IgM or clinically significant disease parameters .

# Response Assessments for CHOP-R, CVP-R, or CP-R

| | CHOP-R | CVP-R | CP-R |
|---|---|---|---|
| **(N)** | 23 | 16 | 19 |
| **Overall Responders** | 22 (96%) | 14 (88%) | 18 (95%) |
| **Major Responders (PR or better)** | 16 (70%) | 12 (75%) | 15 (80%) |
| **Complete/Near Complete Responders** | 4 (17%) | 2 (12%) | 0 (0%) |
| **Median Change in sIgM (%)** | -83.2% | -65.5% | -56.2% |
| **Improvement in Hct ( >2%)** | 19 (83%) | 11 (68%) | 12 (63%) |
| **Time to Progression (months)** | 19 | >35 | >20 |

# Kaplan Meier Curve



# Inferior outcome associated with higher IgM levels in CHOP-R treated patients.

- CHOP-R cohort had a greater number of patients with elevated serum IgM $\geq$ 5,000 mg/dL;
- Overall and complete responses in CHOP-R patients with IgM $\geq$ 5,000 mg/dL (50%; 0%) were inferior to those patients with IgM < 5,000 mg/dL (91%; 36%); p=0.06;
- Time to progression was also shorter in patients with pre-therapy serum IgM levels $\geq$ 5,000 mg/dL versus patients <5000 mg/dL (11.1 vs. 17.8 months); p= 0.42.

Ioakimidis et al, Clin Lymph Myeloma 2009.

# Treatment Related Adverse Events

| | Neutropenic Fever | Hospitalization | Therapy Related Neuropathy | Hemorrhagic cystis |
|---|---|---|---|---|
| **CP-R** | 0% | 0% | 0% | 0% |
| **CVP-R** | 12.5% | 25% | 68.8%[b] | 0% |
| **CHOP-R** | 17% | 13% | 47.8%[a] | 8.6% |

p= not significant (NS) except as follows : (a) and (b) p= <0.001

Ioakimidis et al, Clin Lymph Myeloma 2009.

# Rituximab Related "IgM Flare"

| | IgM Flare | Plasma-pheresis due to IgM Flare |
|---|---|---|
| **CP-R** | 25% | 16% |
| **CVP-R** | 25% | 12.5% |
| **CHOP-R** | 27% | 13.6% |

p= Not significant (NS)

Ioakimidis et al, Clin Lymph Myeloma 2009.

# Summary

- The results of this study demonstrate comparable overall and major response rates among patients who received CHOP-R , CVP-R and CP-R;
- Neuropathy was significantly more pronounced in patients who received CHOP-R and CVP-R versus CP-R;
- The incidence of febrile neutropenia and hospitalizations was also higher in patients treated with CHOP-R and CVP-R versus CP-R;
- The addition of doxorubicin and/or vincristine did not prevent rituximab induced “IgM flare” and interventional plasmapheresis.

# Summary

- The use of doxorubicin and vincristine sparing regimens such as CP-R or R-DC may represent reasonable treatment options to more intense cyclophosphamide based regimens while minimizing treatment related complications.

- Randomized studies to address the optimal cyclophosphamide based rituximab combinations are warranted.

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