Anti-HCV therapy in HCV-related NHL

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Questions about HCV+ in NHL

- Is the NHL related with HCV infection ?
- Which is the best therapeutic strategy ?
- Is the antiviral treatment appropriate ?
- Is the chemotherapy safe ?
- The outcome of HCV+NHL is the same as compared with the HCV- ?
- Which is the role of anti-CD20 ?

Is the NHL related with HCV infection ?

Clinical characteristics:

- **Histological subtype**
  - **Lymphoplasmacytic**
  - **Primary nodal marginal zone**
  - **Splenic marginal zone**
  - **MALT marginal zone**
- **Indolent course**
- **Presence of mixed cryoglobulinemia**
- **Presence of autoimmunity**
- **Presence of monoclonal IgMk component**

Biological characteristics:

- **Since the primary target of antibody responses is the HCV-E2 protein the antibodies derived from HCV-infected patients use a restricted IgV gene repertoire, with a strong bias for V_H1-69 (also known as 51p1) and V3-A27 (also known as 325).**
- **The monoclonal IgM component of type II MC is often encoded by the same set of V region genes, V_H1-69 and V_k3 -A27**
- **bcl-2/IgH translocation**

Which is the best therapeutic strategy ?

Factors to be taken in consideration:

• **Tumor burden**	**High (chemotherapy)**	**Low (antiviral)**
• **Disease course**	**Aggressive (chemoterapy)**	**Indolent (antiviral)**
• **Liver disease**	**Absent (chemotherapy)**	**Present (antiviral)**
• **Symptoms**	**Tumor-related (chemotherapy)**	**MC-related (antiviral)**
• **Comorbidities**	**Any contra-indication to antiviral therapy**	**(chemotherapy)**
	Any contra-indication to chemotherapy	**(antiviral therapy)**

When the antiviral treatment is appropriate ?

Ideal patient:

Histological subtype typical for HCV-related lymphoma
Indolent course
Low tumor burden
MC-related symptoms
No contra-indications to antiviral therapy
Non-1 HCV genotype

The ideal patient does not exist ….

….. most patients are in a grey zone with some factors for and others against antiviral therapy.

Help from published data?

The antiviral therapy in HCV+NHL : a help from publications ?

- *Vallisa et al. J Clin Oncol 2005*: 13 cases: one follicular lymphoma, 4 lymphoplasmacytoid lymphomas, and 8 marginal-zone lymphomas

  Results: 7 CR and 2 PR but all responders relapsed from 2 to 29 months after the end of the treatment. The hematologic response was related to the disappearance of viremia

- *Pozzato et al. Br J Hematol 2009:* 18 cases: one follicular lymphoma, 10 lymphoplasmacytoid lymphomas, and 7 marginal-zone lymphomas

  Results: 9 CR and 3 PR, a fraction (3 cases) of CR relapsed immediately after the end of treatment. The hematologic response was related to the disappearance of viremia

The antiviral therapy in HCV+NHL : a help from publications ?

- Very small number of cases enrolled
- Heterogeneous histology
- Different treatment schedules
- Scattered presence of mixed cryoglobulinemia
- HCV-associated chronic liver disease of different severity
- Difficult interpretation of the results
- A fraction of patients previously treated with chemotherapy

In conclusion: no help from published data !

At least ….. the treatment is well tolerated: in both studies most patients (80%) completed the therapy; complete and durable response is achieved in a very small fraction of cases

The antiviral therapy in HCV+NHL : The splenic lymphoma with villous lymphocytes

Immunophenotype:

CD19 +

CD20 +

CD22 +

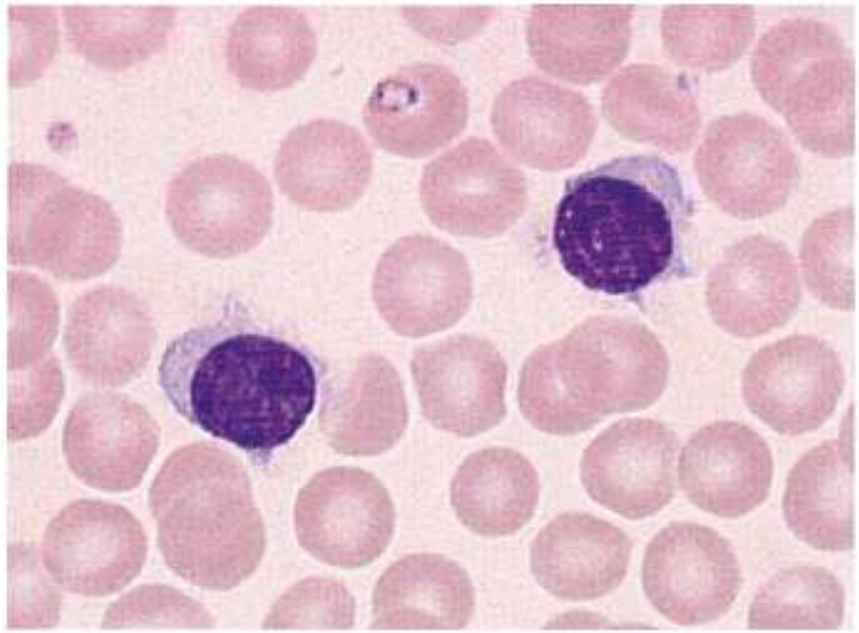
CD24 +

DBA44 +

negative for CD5

negative for CD10

negative for CD25



The splenic lymphoma with villous lymphocytes

❖*Hermine et al. NEJM 2002*

Nine HCV+ cases treated with IFN or IFN+RIBA and compared with 6 HCV-cases with the same therapy

All HCV+ cases responded to treatment while none of the HCV- showed any response. After a mean of 27 months of follow-up 7 cases were still negative for HCV-RNA

❖ *Kelaidi C et al. Leukemia 2004*

8 cases treated with combination therapy: 5 long term responders. Viral and hematological responses were associated.

The splenic lymphoma with villous lymphocytes

- *Saadoun D et al. Blood 2005*
  18 cases (all showing MC) treated with IFN and Riba:14 complete hematological and virological responders.

- *Kanbay M et al Am J Hematol 2006*
  One case treated with peginterferon: complete responder

- *Nunes J et al. Acta Med Port 2010*
  One case treated with PEG-IFN plus Riba: complete responder

Conclusions from these papers:
Small number of cases, but very homogeneous for histology, clinical and biological characteristics.
Antiviral treatment safe and effective !

Is the chemotherapy safe in HCV+ NHL ?

Acute hepatic toxicity during cyclic chemotherapy in non Hodgkin's lymphoma.

Faggioli et al. Haematologica 1997

…we did not detect acute hepatitis due to the reactivation of HCV replication.

Prevalence of hepatitis B and C virus infection in haematological malignancies and liver injury following chemotherapy

Takai et al. European J Hematol 2005

…. The incidence of post-chemotherapy liver injury in 25 HBV carriers (36.0%) was significantly higher than that in 539 non-hepatitis virus carriers (12.6%) and 37 HCV carriers (10.8%).

Distinctive natural history in hepatitis C virus positive diffuse large B-cell lymphoma: analysis of 156 patients from northern Italy

Visco et al. Ann Oncol 2006

…. 156 previously untreated consecutive HCV-positive patients with DLBCL. Only five patients (4%) had to discontinue chemotherapy for severe liver function impairment

Is the chemotherapy safe in HCV+ NHL ?

Impact of treatment-related liver toxicity on the outcome of HCV+ NHL

Arcaini et al. Am J Hematol 2010

….. 160 patients with NHL and HCV infection (99 with DLCL and 3 MCL and the others with indolent NHL)

Among 93 patients with normal ALT, 16 patients (17%) developed liver toxicity

Among 67 patients with abnormal basal ALT, 8 (12%) had liver toxicity

In conclusions

In HCV+ NHL the chemotherapy is safe and only a small fraction of cases (less than 10%) develop hepatic toxicity. Only in a minority of patients (2-5%) the treatment must be stopped for severe liver toxicity.

The liver toxicity is rather related with the underlying chronic liver disease than an increase of HCV replication .

The outcome of HCV+NHL is the same as compared with the HCV- ?

- **Clinical features and outcome in HCV-positive aggressive non-Hodgkin's lymphoma.**

  Tomita N et al Leukemia Lymphoma 2003

  …. patients with HCV+ aggressive NHL have a similar prognosis as HCV- aggressive NHL …. At least in non-cirrhotic subjects

- **Characteristics and outcome of diffuse large B-cell lymphoma in HCV+ patients in LNH 93 and LNH 98 GELA programs**

  Besson C et al. J Clin. Oncol 2006

  Low prevalence of HCV infection: 26 cases (over 5,586 NHL: 0.46%). The proportion of high and high-intermediate IPI was higher among HCV-positive patients. At 2 years, the OS of HCV+ cases was 56% vs 80% of their matched patients and PFS was 53% vs 75%.

- **Distinctive natural history in hepatitis C virus positive diffuse large B-cell lymphoma: analysis of 156 patients from northern Italy**

  Visco et al. Ann Oncol 2006

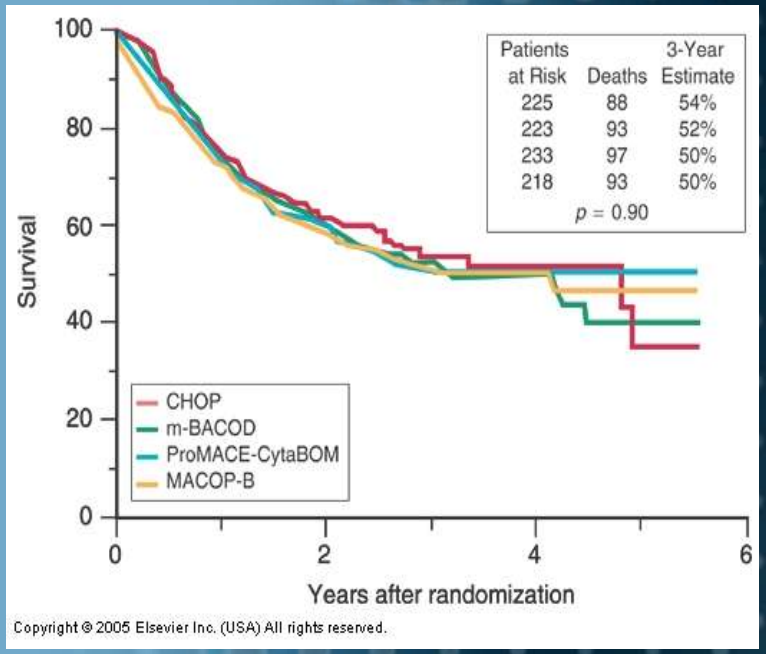
  The OS and PFS of HCV+ cases were similar to HCV- cases. These series comprises 28 cases treated with antiCD20, therefore there are not absolute contraindications to the use of monoclonal antibodies in the treatment of HCV+ NHL.

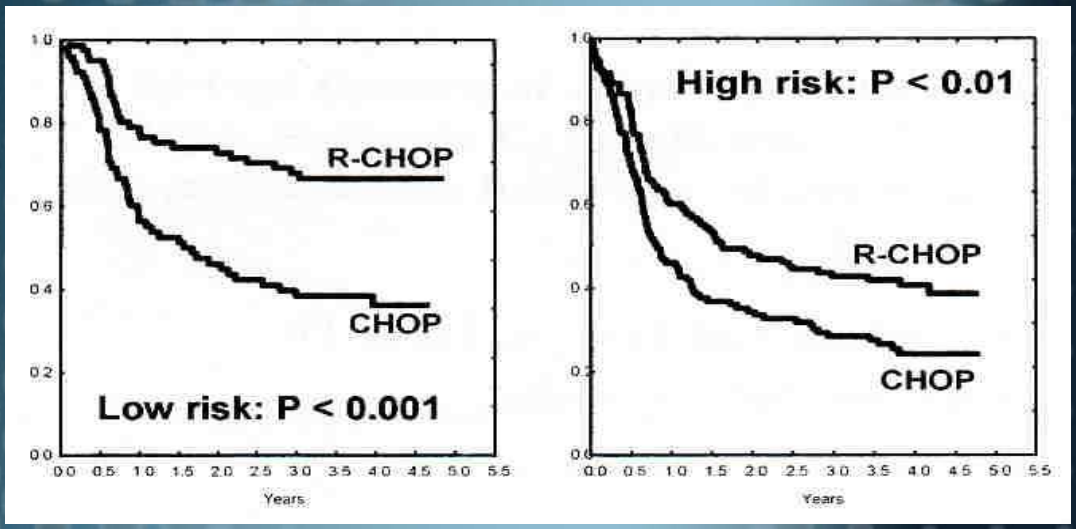
Rituximab in HCV+ MC and NHL

- From 1999 (Zaja et al. Haematologica) and 2011 february, 80 full paper-letter-review have been published. Most of them indicate that anti-CD20 treatment is safe and effective in MC (in both HCV+ and HCV- cases).

- Recently, anti-CD20 were used even in 19 cases of MC with advanced/end-stage liver disease. Together with a relief from MC syndrome, improvement in liver protidosynthetic activity and ascites degree was observed (Zignego AL et al. Blood 2010).

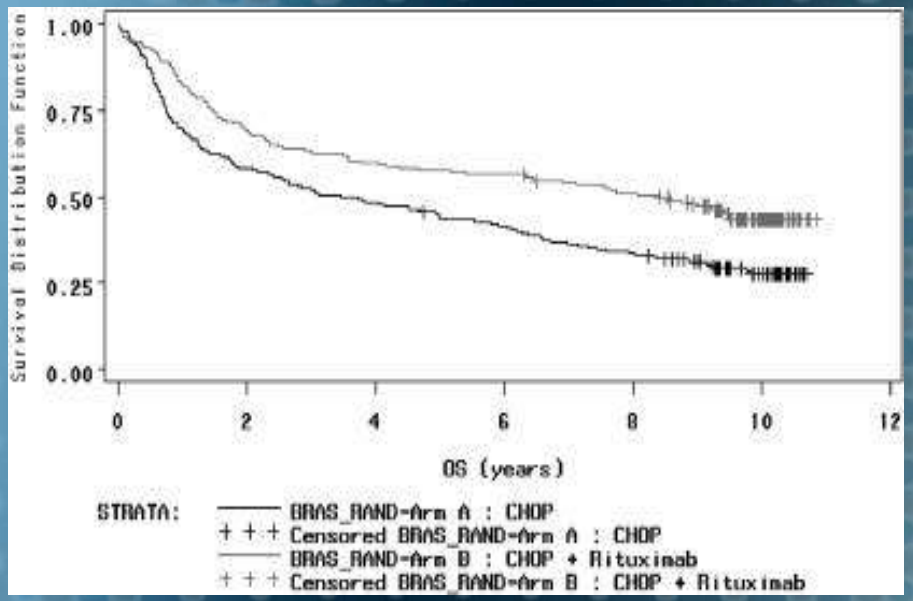
All these reports indicate that anti-CD20 is safe and effective in MC, despite an increase in the HCV-RNA concentrations.

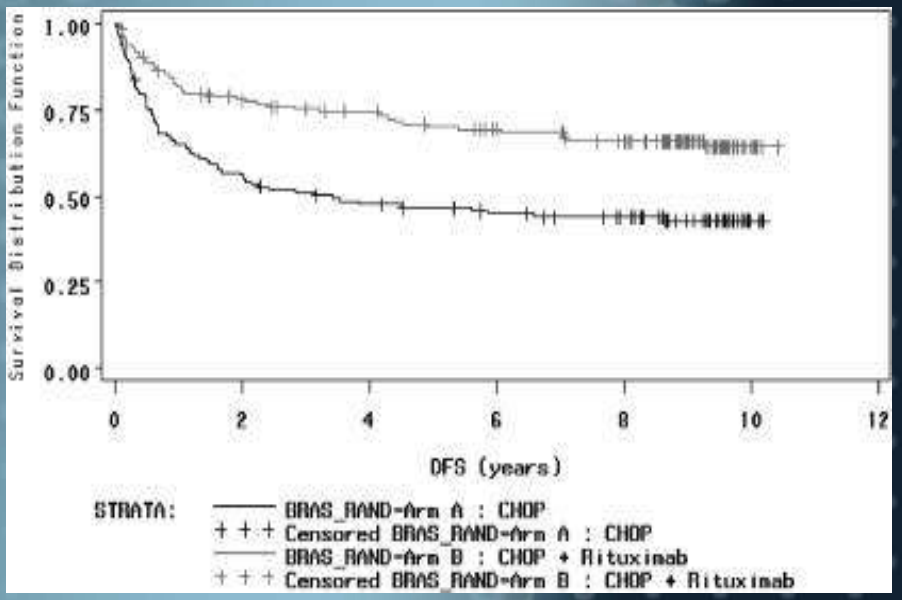




Coiffier B et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with DLBCL N Engl J Med. 2002; 346(4):235–242.

Coiffier B et al Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients Blood. 2010 September 23; 116(12): 2040–2045.





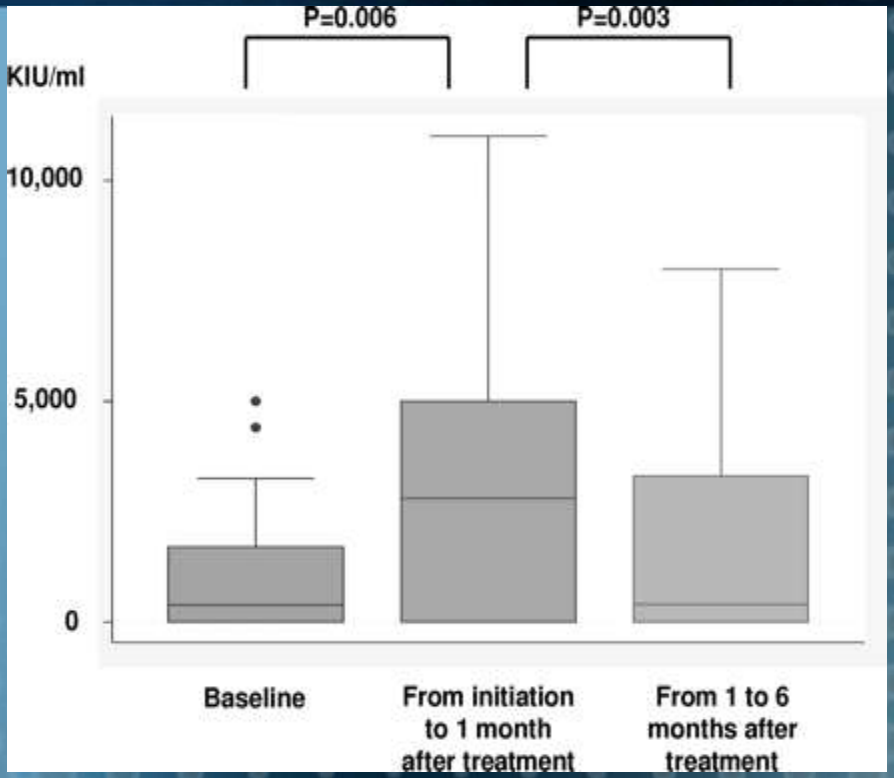
Chemotherapy Combinations With Monoclonal Antibodies in Follicular Lymphomas
Kahl B Semin Hematol 2010

Study Group	Regimen	N° cases	Follow-up	PFS		OS	
				R-Chemo	Chemo	R-Chemo	Chemo
GLSG	CHOP	428	2 year	82%	64%	95%	90%
GELA-GOELAMS	CHVP-IFN	358	3.5 year	67%	46%	91%	84%
International	CVP	321	4 year	54%	17%	83%	77%
OSHO	MCP	201	4 year	71%	40%	87%	74%

GLSG, German Low Grade Lymphoma Study Group;
ELA, Group d'Etude des Lymphomas de l'Adulte;
GOELAMS, Groupe Ouest Est des Leucemies et Autres Maladies du Sang;
OSHO, East German Study Group Hematology and oncology.

Since most NHL are currently treated with chemotherapy combined with anti-CD20, a fraction of these patients are HCV+ and no large-scale studies has been performed to investigate the influence of HCV infection on hepatic toxicity in patients with NHL treated with rituximab-containing chemotherapy

Information from multicenter Japanese study: Ennishi et al. Blood Dec 2010; 116(24):5119-25



553 patients, 131 of whom were HCV+ with DLBCL were treated (R-CHOP or R-CHOP–like chemotherapy.

CR rates were 81% and 83% in HCV+ HCV- cases respectively

Of the 131 patients who were HCV+, 36 (27%) had severe hepatic toxicity, compared with 3% of those who were HCV-. Mean HCV-RNA levels increased during therapy (P = .006) but then decreased afterward.

To note: 57 (43%) and 20 (15%) patients had chronic hepatitis and cirrhosis respectively. HCC was detected in 7 patients (5%) before therapy

Rituximab in HCV+ NHL

Ennishi et al. Blood Dec 2010; 116(24):5119-25

Of the 131 patients who were HCV+, 36 (27%) had severe hepatic toxicity, compared with 3% of those who were HCV-
The hepatic toxicity was not associated with poor PFS or OS

6 patients died due to hepatic failure (4 had HCC and 2 LC with portal hypertension)

CR rates were 81% and 83% in HCV+ and HCV- cases respectively
No difference was observed in PFS according to HCV infection (3-year 69% vs 77%)

Rituximab in HCV+ NHL

CONCLUSIONS

Since several studies highlighted the possibility of a high incidence of severe hepatic toxicity in patients who were HCV-positive, hepatic function should be carefully monitored in patients who are HCV-positive and receive immunochemotherapy.

Rituximab in safe in HCV+NHL and, given it's efficacy to improve OS and PFS, it should be used in HCV+NHL as well as in HCV-NHL