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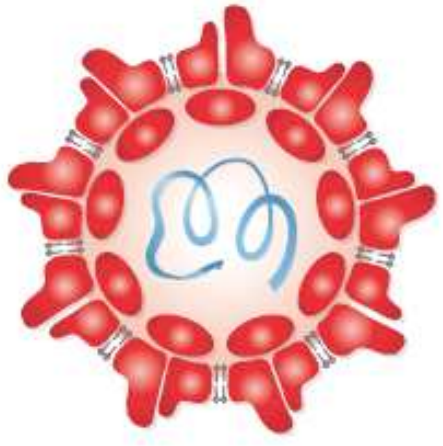

Giornata di Aggiornamento su:
LE INFEZIONI DA VIRUS DELL'EPATITE C (HCV)
14 ottobre 2011

HCV e patologie onco-ematologiche

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BACKGROUND

- **Hepatitis C virus (HCV) infection is a major public health problem worldwide, with a global prevalence of 170 million people affected.**

- **HCV has been associated with several immune-mediated process, including hematological disorders .**

- **In this sense, HCV shows lymphotropism and its replication in peripheral blood mononuclear cells may be etiologically implicated in certain lymphoproliferative diseases.**

Manifestazioni epatiche	Manifestazioni extraepatiche
EPATITE CRONICA	CRIOGLOBULINEMIA MISTA
CIRROSI	GLOMERULONEFRITE
EPATOCARCINOMA	PORFIRIA CUTANEA TARDA
	AUTOANTICORPI
	EPATITE AUTOIMMUNE (?)
	LINFOMI NON-HODGKIN (?)

HCV

Virus as cause of neoplasia

Experimental evidences

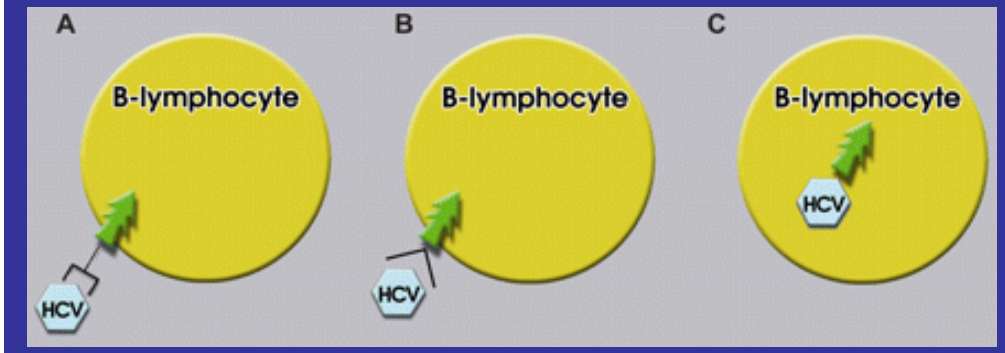
1. Capacity of transforming human cells in vitro
2. Viral genome only in the tumour and not in normal cells
3. Capacity of inducing tumour in animal model

Epidemiological evidences

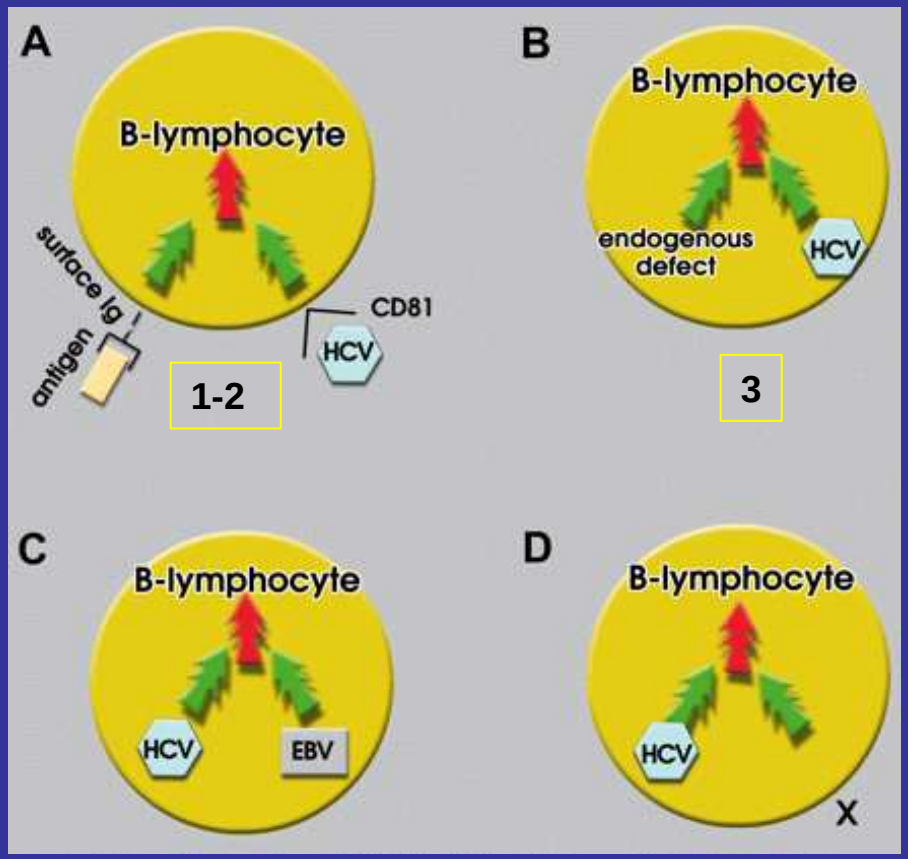
1. Overlapping geographic distributions of infection and of neoplasia
2. Viral markers more frequent in patients with neoplasia
3. Viral markers detected before diagnosis of neoplasia
4. Higher incidence of neoplasia in infected subjects
5. Infection prevention reduces incidence of neoplasia

Evans and Mueller Ann Epidemiol 1990

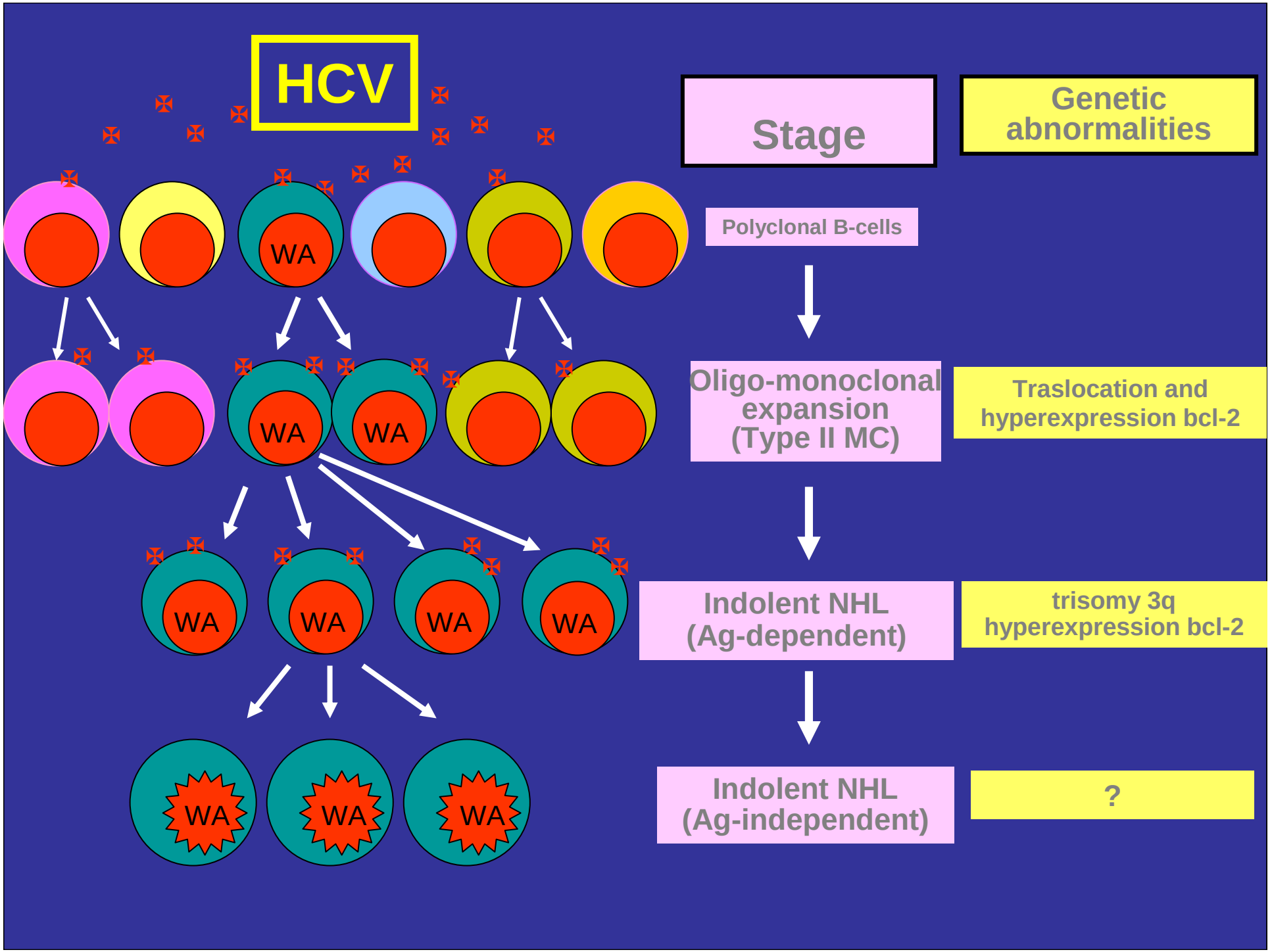
Three pathways for HCV-induced lymphomagenesis and integration of an HCV-derived oncogenic signal with an HCV-independent one



1. Chronic antigenic stimulation of a B cell that interacts through its surface Igs with the cognate HCV Ag
2. HCV-E2 protein engaging its high-affinity receptor CD81 expressed on B cells
3. Direct infection of a B cell by HCV



F Marcucci and A Mele, Blood, 2011


HCV
WA
WA
WA
WA
WA
WA
WA
WA
WA
Stage
Genetic abnormalities
Polyclonal B-cells
Oligo-monoclonal expansion (Type II MC)
Traslocation and hyperexpression bcl-2
Indolent NHL (Ag-dependent)
trisomy 3q hyperexpression bcl-2
Indolent NHL (Ag-independent)
?

ASSOCIATION OF HCV AND NHL

HCV and NHL: epidemiological studies

COHORT STUDIES: development of lymphoma in cohorts of HCV+ subjects (only 4 studies)

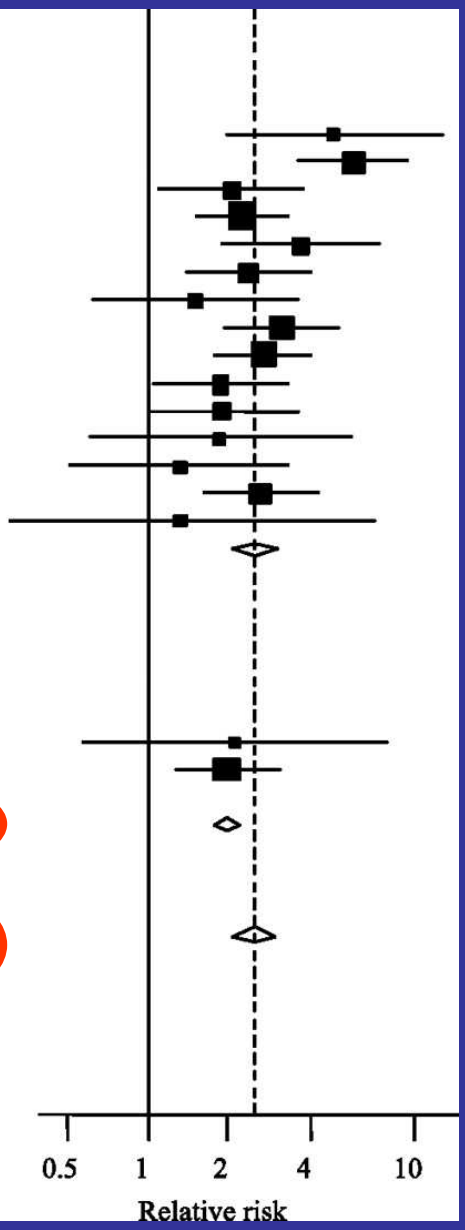
- Japan 1999: positive association
- Sweden 2005: positive association with NHL, and myeloma
- USA 2002: negative association
- USA 2007 (Veterans): assoc. positive (Cryo, NHL, MW)

CASE-CONTROL STUDIES: Comparison of the prevalence of HCV among NHL cohorts and control cohorts (lymphoproliferative diseases other than lymphoma, solid tumors, patients undergoing biopsy or colonoscopy, healthy blood donors, samples of reference population) (approximately 15 studies)

Metanalysis 2006

	Cases HCV+/HCV-	Controls HCV+/HCV-	RR	95%CI
Zuckerman, 1997 (USA)	26/94	6/108	4.98	1.96-12.65
Vallisa, 1999 (Italy)	65/110	32/318	5.87	3.65- 9.44
Mizorogi, 2000 (Japan)	17/117	34/482	2.06	1.11- 3.82
Pioltelli, 2000 (Italy)	48/252	66/781	2.25	1.51- 3.35
Montella, 2001 (Italy)	28/83	17/209	3.70	1.90- 7.20
Imai, 2002 (Japan)	23/164	(10)	2.39	1.41- 4.05
Kim, 2002 (S.Korea)	7/207	19/846	1.51	0.63- 3.62
Mele/Bianco, 2003/2004 (Italy)	83/447	22/374	3.16	1.93- 5.15
Cowgill, 2004 (Egypt)	94/126	52/170	2.70	1.80- 4.05
De Sanjosé, 2004 (Spain)	25/351	22/577	1.87	1.04- 3.36
Engels, 2004 (USA)	32/781	14/670	1.89	1.00- 4.00
Morton, 2004 (USA)	8/456	5/529	1.86	0.60- 5.77
Séve, 2004 (France)	6/206	20/954	1.31	0.51- 3.37
Talamini, 2004 (Italy)	44/181	[illegible]	2.64	1.62- 4.30
Vajdic, 2006 (Australia)	3/594	2/520	[illegible]	0.22- 7.92
All case-control studies	**509/4169**	**366/6997**	**2.52**	**2.08- 3.05**
Test of heterogeneity between studies: χ^2(14df)=[illegible]; p<0.01				
Cohort studies	**(Observed)**	**(Expected)**		
Rabkin, 2001 (USA)	0/57	0/95	-	-
Oshawa, 1999 (Japan)	(4)	(2)	2.10	0.57- 7.74
Duberg, 2005 (Sweden)	(24)	(12)	[illegible]	[illegible] 3.09
All cohort studies	**(28)**	**(14)**	**1.98**	**1.79- 2.19**
Test of heterogeneity between studies: χ^2 (1df)= [illegible]				
All			**2.50**	**2.08-3.01**

Test of heterogeneity between study design: χ^2 (1df)=606; p<0.01



Dal Maso, Cancer Epidemiol Biomarkers Prev ,2006

HCV and NHL

- NHL attributable to HCV in countries with high incidence: 10%
- NHL attributable to HCV in countries with low incidence: <1%
- The association with HCV is present and of similar magnitude in all NHL subgroups
- The epidemiological evidence alone can not determine whether the association is causal

Dal Maso, Cancer Epidemiol Biomarkers Prev, 2006

Studio italiano caso-controllo

- 400 pz con LNH e 396 controlli
- LNH HCV+: **17,5%**
- Controlli HCV+: **5,6%**
- Su 205 LNH a grandi cellule: 19% HCV+
- Su 15 MZL splenici e nodali: 26,6% HCV+
- Su 25 MZL del MALT: 12% HCV+

Mele et al Blood 2003

Studio italiano caso-controllo

- Rischio relativo

tutti	**3,1**
indolenti	**2,3**
aggressivi	**3,5**

- Casi attribuibili ad HCV **4,6%**

Mele et al Blood 2003

International Lymphoma Epidemiology Consortium (InterLymph)

- *Pooled case-control study* (4,784 NHL and 6,269 controls)
- HCV infection in 172 cases of NHL (3.6%) and 169 (2.7%) controls, OR 1.78
- HCV is associated with:

  Marginal zone lymphoma (OR, 2.47)

  Diffuse large B cell lymphoma (OR 2.24)

  Lymphoplasmocytic lymphoma (OR 2.57)

de Sanjose S et al Clin Gastroenterol Hepatol. 2008

HCV
not only a problem, also an opportunity

A problem (aggressive lymphomas)

- Toxicity

- Exclusion from clinical trials (often for medical decision)

An opportunity (indolent lymphoma)

- Peculiar model of antigen-driven lymphoma

- Possible targeted therapy:

In subjects with HCV + NHL regression of indolent lymphoma after **antiviral therapy** is the strongest argument in favor of the etiological role of virus.

Indolent lymphomas

WHO classification 2008

MARGINAL ZONE LYMPHOMAS

- Splenic MZL +/- villous lymphocytes
- Primary nodal MZL
- Extranodal MZL MALT-type

NON-MARGINAL ZONE LYMPHOMAS

- Follicular lymphoma
- Lymphoplasmacytic lymphoma/WM
- Lymphocytic lymphoma

SMZL: an indolent lymphoma (?)

- 2% of all NHL

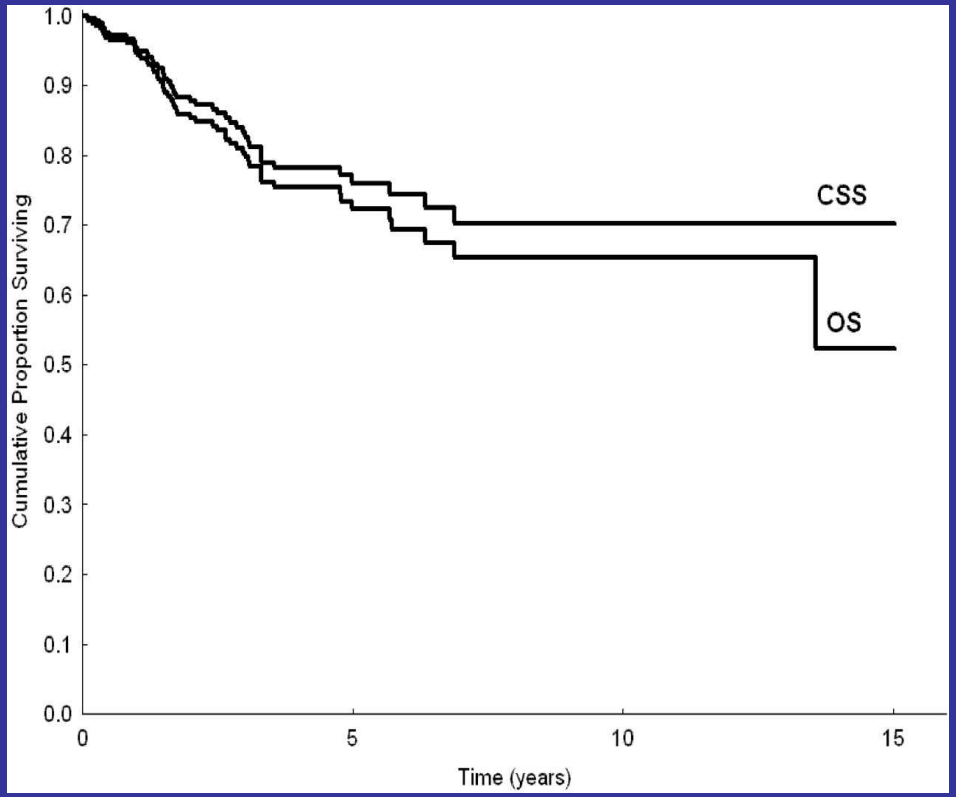
- Symptomatic splenomegaly is the presenting feature in almost all patients

- Median overall survival exceeding 10 years

- More aggressive course in a significant subset of patients

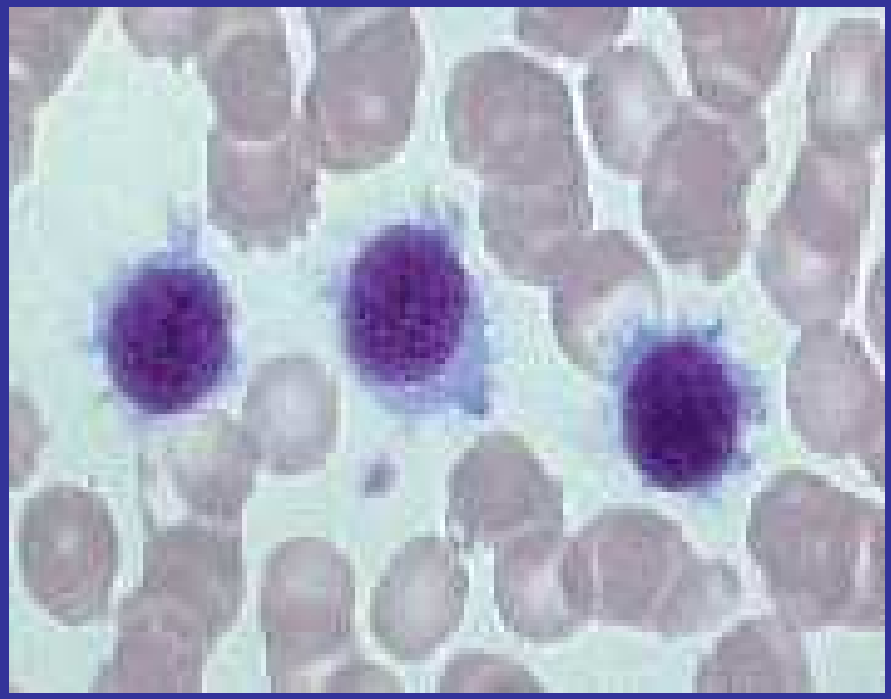
- Hot issues: When, how and how much to treat ?

Arcaini & Paulli Haematologica, 2010



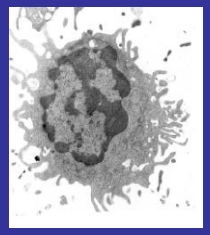
Arcaini et al Blood , 2006

Morphology



- Loss of villi if not a proper coloration
- No agreement on the percentage for dg
- Cytological diagnosis is not feasible
- WHO: + / - villous lymphocytes

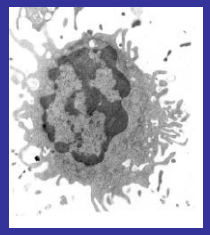
- Villous lymphocytes also in other lymphoma subtypes
- Possible morphologic heterogeneity



HCV prevalence in 255 pts with SMZL and available serology

	%
HCV+	19
HCV genotype	
1b	67
2b	7
2a/2c	26

Arcaini et al Blood , 2006



SMZL: HCV infection

	HCV-	HCV+	p
	N. = 206	N. = 49	
Nodal disease	41%	57 %	0.05
Abdominal LN	22 %	43 %	0.006
Liver involvement	16 %	18 %	
B symptoms	21 %	4 %	0.003
Serum MC	19 %	**40 %**	0.005
Cryoglobulins	1 %	**40 %**	<0.0001

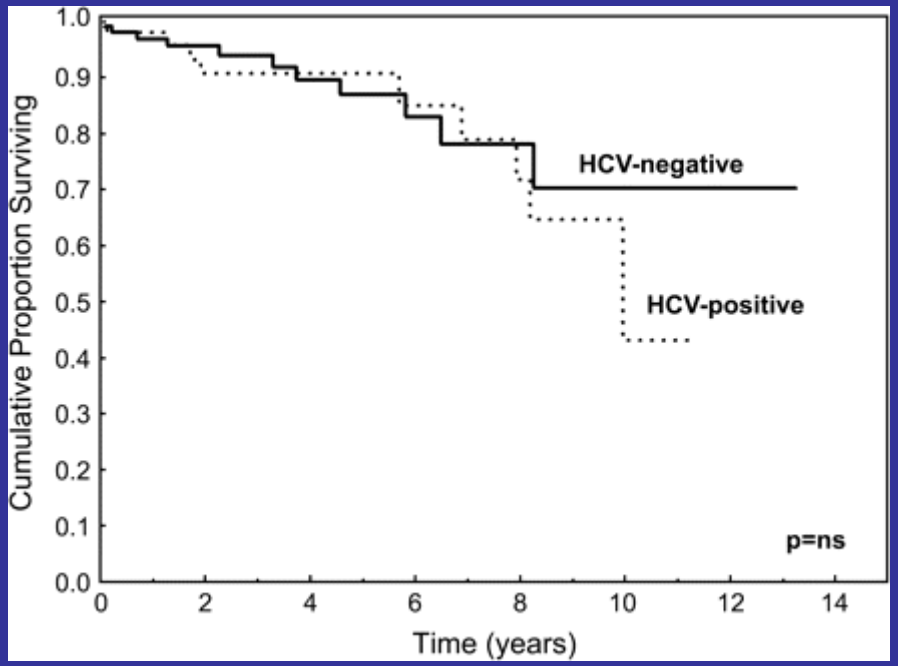
Arcaini et al Blood , 2006

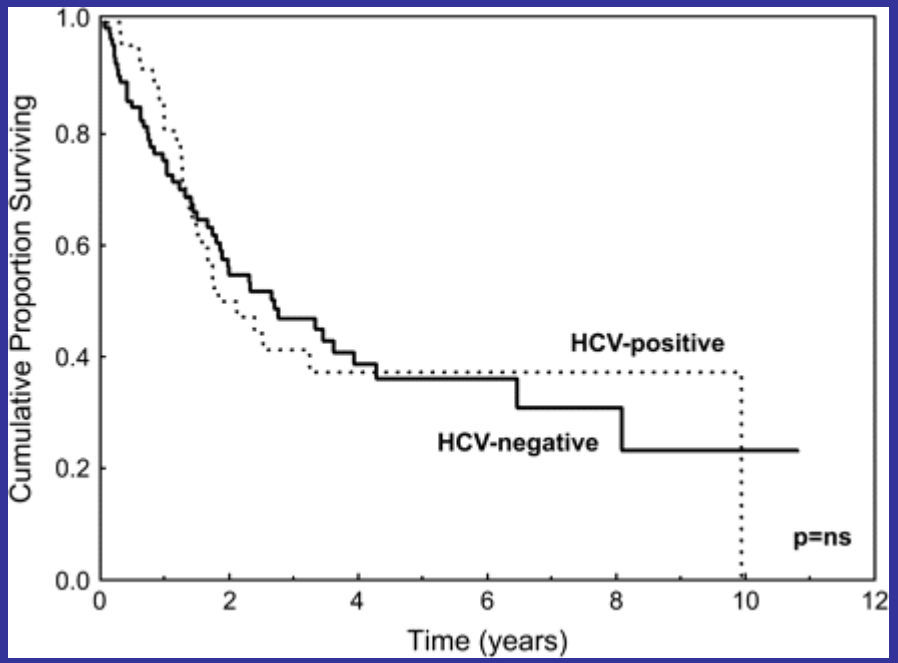
EXTRANODAL MARGINAL ZONE LYMPHOMA

MALT sites and HCV

MALT organ	HCV+	%
Single MALT site	58/156	37%
Skin	21/49	**43%**
Salivary glands	15/32	**47%**
Ocular adnexa	9/25	**36%**
Waldeyer's ring	3/22	14%
Lung	3/13	23%
Breast	4/6	67%
Liver	1/3	33%
Other sites	2/10	20%
Multiple MALT sites	2/16	13%

OS and EFS according to HCV



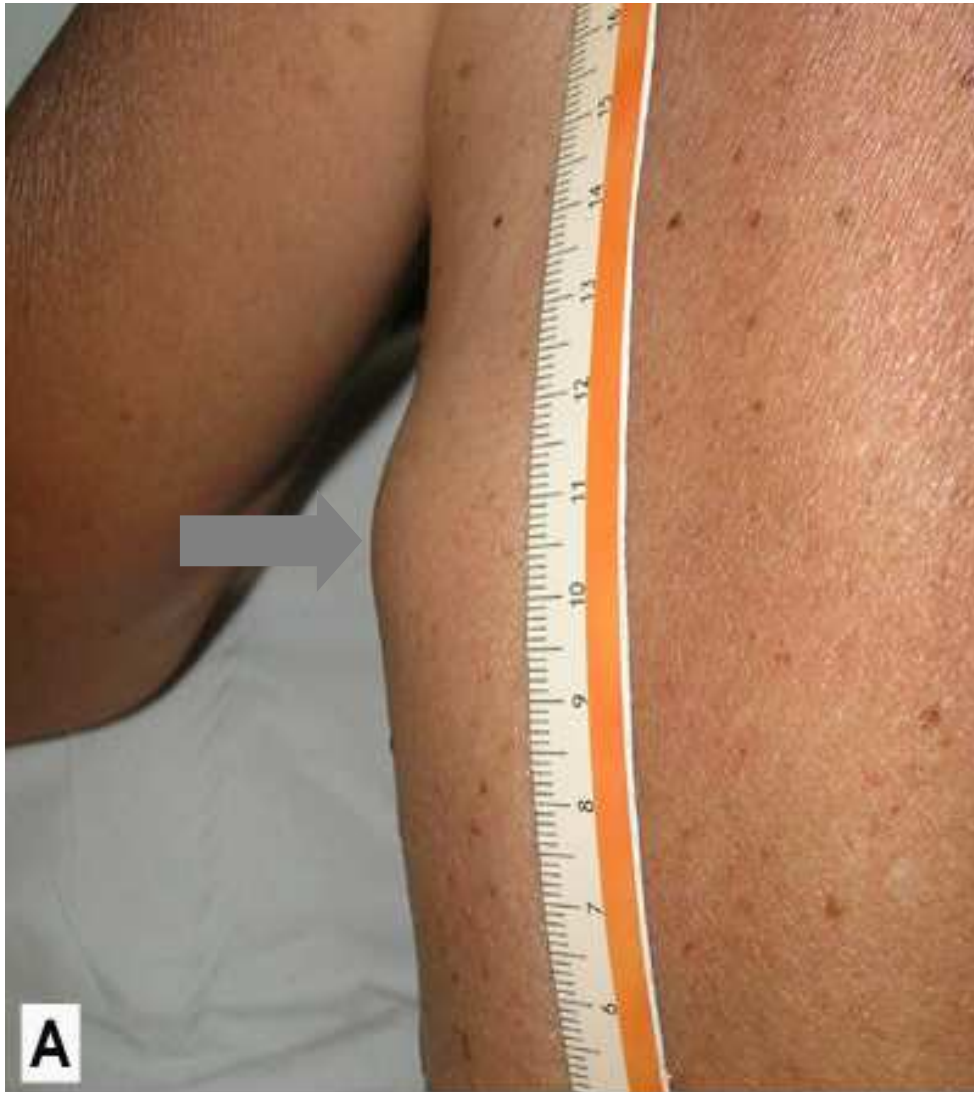


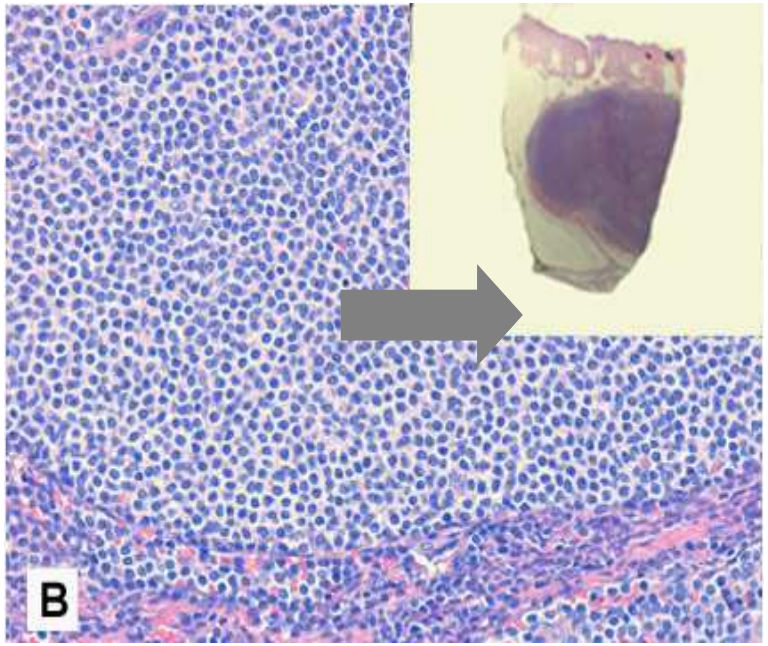
L Arcaini et al, Ann Oncol, 2007

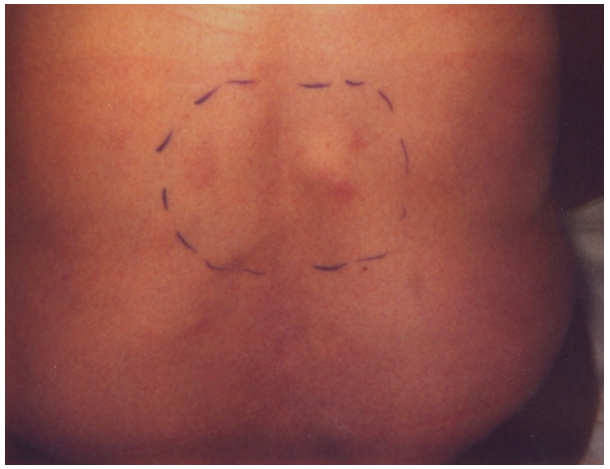
MALT lymphomas and HCV

- High HCV prevalence (35%)
- HCV+: unique MALT site
- Specific HCV-related MALT NHL ?

Lipoma-like marginal zone lymphoma







HCV status

- **HCV serology: 12/12 positive**
- **HCV-RNA+ 10/10**
- Genotype: 2a/2c in 5, 2a in 1, 2b in 1
- Cryoglobulins in 4 pts
- 2 pts with cryoglobulinemic purpura
- No pt with autoimmune disease

Paulli et al, Annals of Oncology 2010

Therapy and Outcome

- Surgical excision: 12 pts
- Observation: 3 pts
- Local RT: 2 pts
- Chlorambucil: 2 pts
- CHOP-like + RT: 3 pts
- Rituximab: 1 pt
- IFN + ribavirin: 1 pt
- CR: 5 pts; PR: 4 pts
- Rituximab: CR for 2 yrs; CR2 for 20 months

After median follow up of 50 months, 11 pts alive,
1 pt died 11 yrs after appearance nodule and 7 yrs after diagnosis

Paulli et al, Annals of Oncology 2010

Antiviral therapy

- A male patient of 68 years: IFN + Ribavirin → RVR and CR (obtained slowly) for lymphoma for 1 year

- A female patient of 62 years:

CHOP + RT →: CR for 20 months

IFN for 6 months → CR after 1 month and virological response

At 8 months after the end of treatment HCV-RNA+

Appearance of new nodules 3 months after HCV-RNA returned positive

ANTIVIRAL THERAPY

Splenic lymphoma with villous lymphocytes

9 pts with SLVL and HCV infection

- IFN-a 3 MU 3 times/week for 6 months
- 7 → HCV-RNA- + CR
- 2 NR → Ribavirin → HCV-RNA- 1 CR, 1 PR
- 1 relapse with HCV-RNA+
- No molecular response

6 pts with SLVL HCV-neg: NR

Hermine et al, NEJM, 2002

Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity?

- 18 pts with SLVL
- Median age 58 years
- Predominantly female (F 78%)
- Symptomatic type II MC : 72%
- Symptoms preceding dg of SLVL in 7 HCV (mean 3.5 years)
- Genotype 1: 54%

Saadoun et al, Blood 2004

Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity?

- Haematological + virological response: 78%
- HCV genotype 1: 54% (4 / 7 responders)
- No molecular response

Saadoun et al, Blood 2004

MZL and other indolent lymphomas and antiviral treatment

- Italian multicenter study.
- 13 pts with indolent B-cell lymphoma.
- PEG-IFN (70 μγ s.c./wk) + ribavirin (1,200 mg p.o./daily) for at least 6 months.
- 11 patients were able to complete the planned treatment in a period ranging from 6 to 12 months.
- **7 CR (58%), 2 PR (ORR: 75%; mean time: 7.7 ± 3.2 months).**
- Correlation hematologic/virologic response.
- Higher virologic response if genotype 2, while hematologic response did not correlate with the viral genotype.
- No molecular response

Vallisa et al, JCO 2005

Age	Histotype	Stage	Extranodal site	Genotype	Cryo
43	Nodal MZL		BM	2a/2c	**No**
67	Nodal MZL		BM	1b	Yes
72	Follicular	IVe	Skin	2a	**No**
55	Plasmocytoid	IV	BM	na	**No**
66	Plasmocytoid	IVe	Liver	2a/2c	Yes
60	Plasmocytoid	IV	BM	na	Yes
60	Plasmocytoid	IV	BM	1b	Yes
44	Splenic MZL		Spleen	1b	**No**
61	Splenic MZL		Spleen, liver	1b	**No**
42	Splenic MZL		Spleen, liver	na	**No**
40	Splenic MZL	IVs	Spleen	2b	**No**
68	MALT MZL		Orbit	1b	**No**
71	MALT MZL		Sinus	1b	Yes

2 CR

2 CR
1 SD
1 PD

1 CR
1 PR

Vallisa et al, JCO 2005

Age	Histotype	Stage	Extranodal site	Genotype	Cryo
43	**Nodal MZL**	IV	BM	2a/2c	**No**
67	**Nodal MZL**	IV	BM	1b	Yes
72	**Follicular**	IVe	Skin	2a	**No**
55	**Plasmocytoid**		BM	na	**No**
66	**Plasmocytoid**		Liver	2a/2c	Yes
60	**Plasmocytoid**		BM	na	Yes
60	**Plasmocytoid**		BM	1b	Yes
44	**Splenic MZL**	IVs	Spleen	1b	**No**
61	**Splenic MZL**	IVs	Spleen, liver	1b	**No**
42	**Splenic MZL**	IVs	Spleen, liver	na	**No**
40	**Splenic MZL**	IVs	Spleen	2b	**No**
68	**MALT MZL**	IV	Orbit	1b	**No**
71	**MALT MZL**	IVe	Sinus	1b	Yes

2 CR
1 PR
1 SD

Vallisa et al, JCO 2005

Marginal zone lymphomas and antiviral therapy

- 8 pz with MZL: 4 SMZL
  2 extranodal MZL
  1 disseminated MZL
  1 leukemic MZL
- (PEG)-IFN +/- ribavirin
- Lymphoma response: 6 CR
- Virologic response: 5 sustained (3 clinic CR)

Kelaidi et al Leukemia 2004

Indolent lymphomas and antiviral therapy

	Year	N° pts	Diagnosis	Genotypes	Cryoglobulinemia	Anti-Viral Treatment	Virologic Response	NHL Response
Bauduer [80]	1996	1	MZL of MALT (oral cavity)	NA	-	α-IFN	1	1 PR
Caramaschi *et al.* [81]	1999	1	MZL of MALT (salivary glands)	NA	-	α-IFN	NA	1 CR
Moccia *et al.* [82]	1999	3	SMZL	NA	-	α-IFN	NA	2 CR
Hermine *et al.* [77]	2002	9	SLVL	NA	6	α-IFN	7	7 CR
Casato *et al.* [83]	2002	1	Leukemic MZL	NA	1	α-IFN	Decreased HCV-RNA	1 CR
Pitini *et al.* [84]	2004	2	SMZL	NA	-	α-IFN	2	2 CR
Tursi *et al.* [85]	2004	16	MZL of MALT (stomach)	NA	-	α-IFN-2b + RBV	11/16	16 CR
Kelaidi *et al.* [86]	2004	8	SMZL (n=4) Disseminated MZL (n=1) Leukemic MZL (n=1) MZL of MALT (ileus) (n=1)	3a (n=1), 5a (n=1) - 1b 4c/4d	8	α-IFN-2b + RBV	5 SVR, 2 PR	5 CR
Vallisa *et al.* [78]	2005	8	SMZL (n=4) NMZL (n=2) MZL of MALT (n=2)	1b (n=2), 2b (n=1) 2a/2c (n=1), 1b (n=1) 1b (n=2)	2	Peg-IFN + RBV	6	5 CR, 2 PR
Svobeda *et al.* [87]	2005	1	MZL of MALT (salivary gland, liver)	2b	-	Peg-IFN + RBV	1	CR
Sandoun *et al.* [36]	2005	18	SLVL	1 (n=7) 2 (n=4) 3 (n=1) 4 (n=1)	18	α-IFN (+ RBV in 10)	14 CR, 4 PR	14 CR, 4 PR
Paulli *et al.* [61]	2009	2	Subcutaneous MZL of MALT	2a/2c 2b	2	Peg-IFN + RBV	2 CR	1 CR, 1 PR

16* studies
≈ 65 pts
CR: 75%

JP Gisbert et al , 2005

12 (5*) studies
≈ 70 pts
CR: 79%

No prospective trials

Arcaini & Bruno, Current Clinc Pharmacol 2010

Histology

	1st line (n=76)		2nd line AT (n=18)	
	N	%	N	%
Marginal zone lymphoma	47	62	10	55
Splenic	24	32	6	33
Nodal	6	8	1	6
Extranodal of MALT	17	22	3	16
Stomach	3		0	
Skin	5		1	
Orbit	1		1	
Liver	2		0	
Other sites	6		1	
Follicular lymphoma	3	4	2	11
Lymphoplasmacytic lymph.	1	1	2	11
Mantle cell lymphoma	0	0	1	6
SLL	0	0	1	6
Low-grade B-cell NHL NOS	25	33	2	11

L Arcaini et al, 11-ICML, 2011

Clinical and virological features

	1st line (n=76)		2nd line AT (n=18)	
	N	%	N	%
AA stage III-IV	70	92	13	72
LDH > UNL	16	21	4	22
β_2-microglobulin > UNL (n=50)	23	57	9	90
Albumin <3.5 g/dl	5	7	2	11
ALT > UNL	30	40	9	50
Serum MC	20	26	9	50
HCV genotype (n=78)				
- 1	26	41	8	57
- 2	35	53	4	29
- 3	2	4	2	14
- 5	1	2	0	0
Cryoglobulins (n=78)	20	32	9	60
Sympt. cryoglobulinemia (n=78)	6	10	7	47

Hematological response

- 6 pts discontinued AT for toxicity or no VR
- No pt interrupted AT for NHL progression

1st line AT

- ORR **77%** (CR 47%, PR 30%), SD 18%
- ORR **85%** MZL vs **78%** non-MZL (p=0.4)
- ORR **79%** SMZL vs **92%** non-splenic MZL (p=0.4)
- SVR 78%
- HR associated to SVR (p <0.001) but not with HCV genotype (1 vs. 2) and the type of AT (IFN vs peg-IFN)

- **2nd line AT**

- ORR **77%** (CR 27%, PR 50%), SD 18%
- SVR 56%

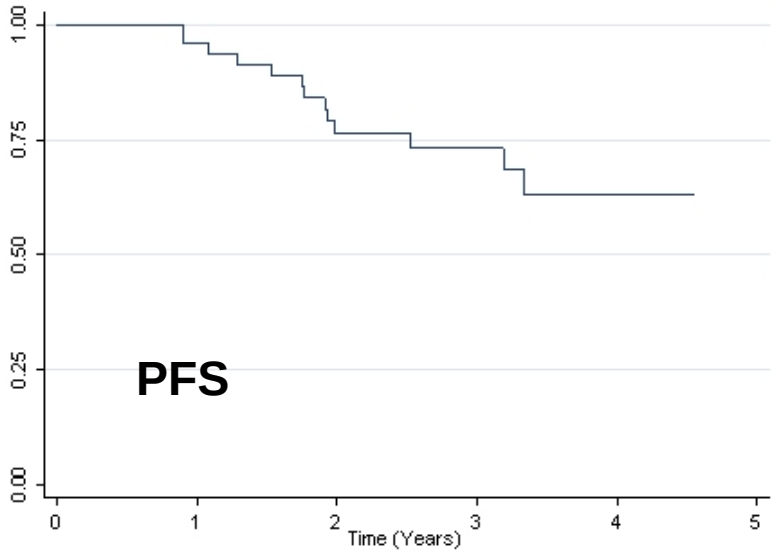
Predictors of response and outcome

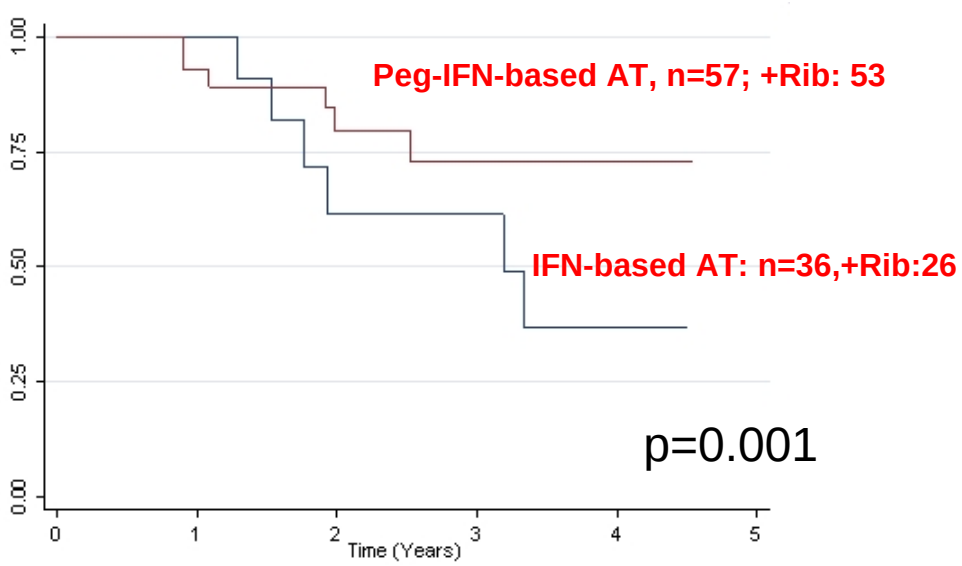
- β_2-microglobulin > UNL and albumin < 3.5 g/dl significantly associated with failure of obtaining HR (respectively p=0.02 and p=0.03)

1st line AT

- 5-yr OS 94%
- 6 pts died (3 for NHL progression, 2 for HCC and 1 for infection)

- DOR > 3 yrs in 40% of pts
- 5-yr PFS 78%
- PFS longer in pts treated with peg-IFN (p=0.001)





Conclusions

- High rates of lymphoma regression in pts with HCV+ indolent NHL treated with AT

- peg-IFN-based AT seems able to guarantee a better long term control of lymphoma

- Lower response rate in second line suggests to employ AT as front-line approach

- To verify whether it is possible to obtain a better long-term control with Rituximab weekly for 4 doses followed by Peg-IFN weekly plus ribavirin daily for 48 weeks (such as in cryoglobulinemia, *Saadoun et al, Blood 2010*)

- New anti-HCV agents and future IFN-free regimens could guarantee AT also for HCV+ NHL pts with controindication to IFN use (age, toxicity)

- AT should be recommended as first-line approach in pts with HCV-related indolent NHL not requiring immediate conventional treatment

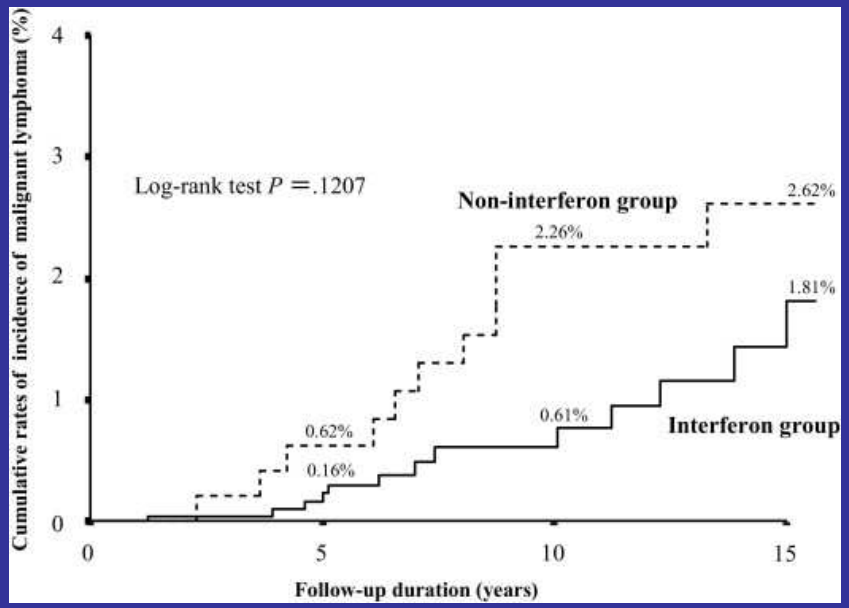
Prognostic models to predict survival in indolent non-Hodgkin's lymphomas associated with hepatitis C virus infection: a multicenter italian study on 1,043 patients on behalf of Fondazione Italiana Linfomi (FIL)

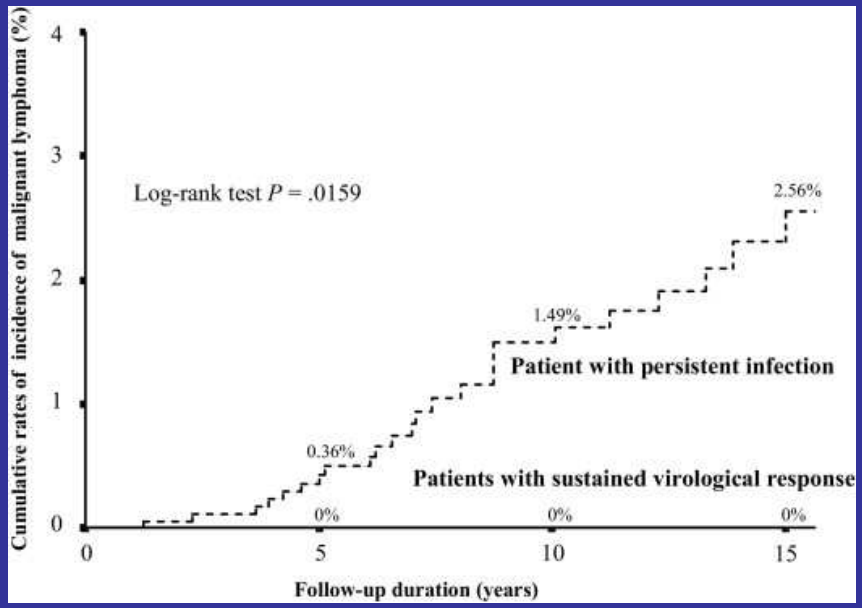
Multivariate analysis for OS (indolent NHL)

	HR	95% CI	p
Age >60 yrs	2.11	1.12 – 3.99	0.005
ECOG ≥2	2.82	1.37 – 5.80	0.02
AA stage III-IV	2.01	1.04 – 3.89	0.04
No AT at any time	**2.56**	**1.32 – 8.22**	**0.01**

Merli et al. Abstract #320 Poster Session II

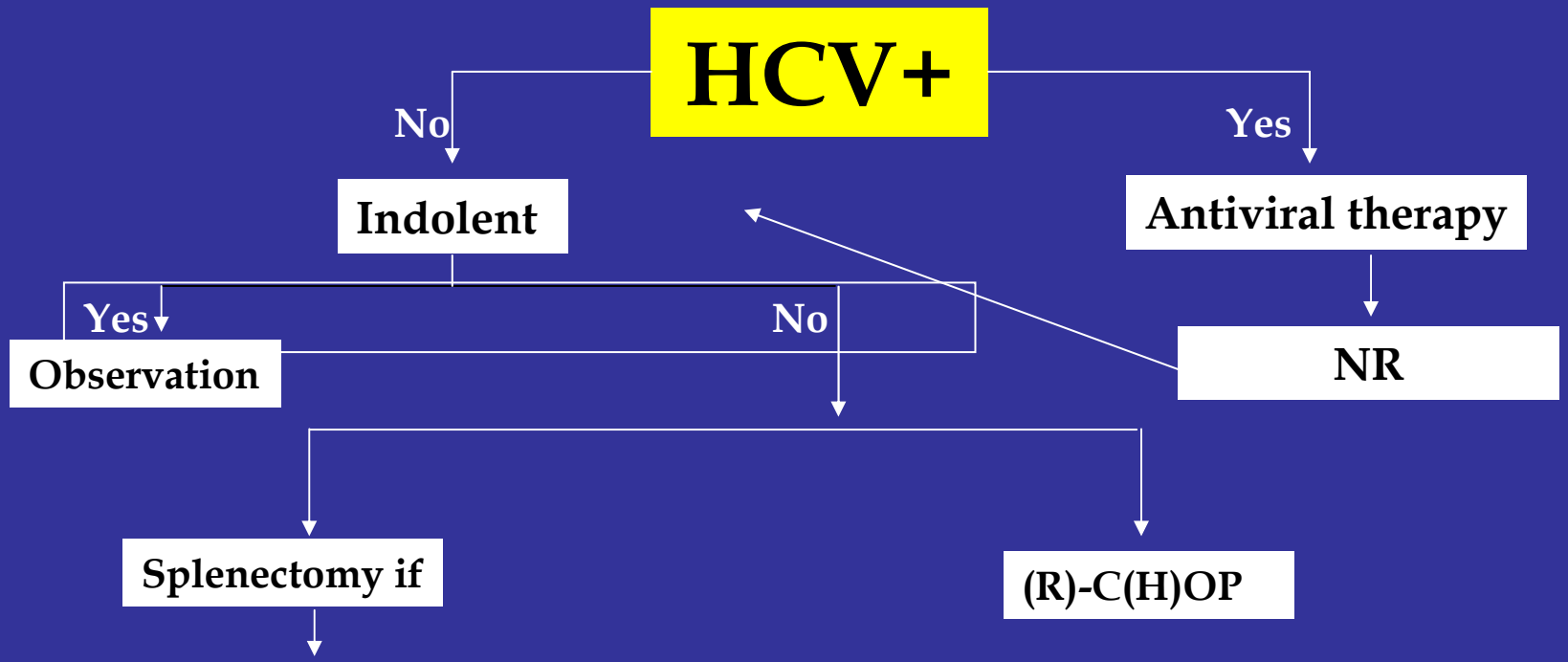
Cumulative rate of the incidence of malignant lymphoma according to treatment and sustained virologic response





Y Kawamura et al, Am J Med, 2007

SMZL: therapeutic algorithm



Symptomatic splenomegaly
- Cytopenia
- Suspected transformation into high grade
- No B symptoms
- No nodal involvement
- Limited BM involvement

Diffuse large B cell lymphoma

HCV
not only an opportuniy, also a problem

A problem (aggressive lymphomas)

- Toxicity

-Exclusion from clinical trials (often for medical decision)

An opportunity (indolent lymphoma)

- Peculiar model of antigen-driven lymphoma

- Possible targeted therapy.

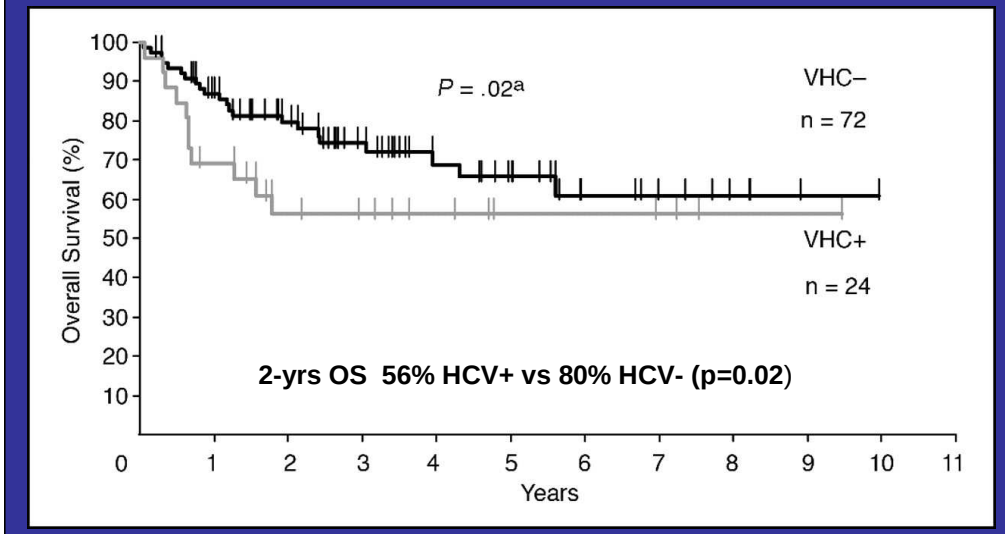
DLBCL and HCV infection: pre-Rituximab era

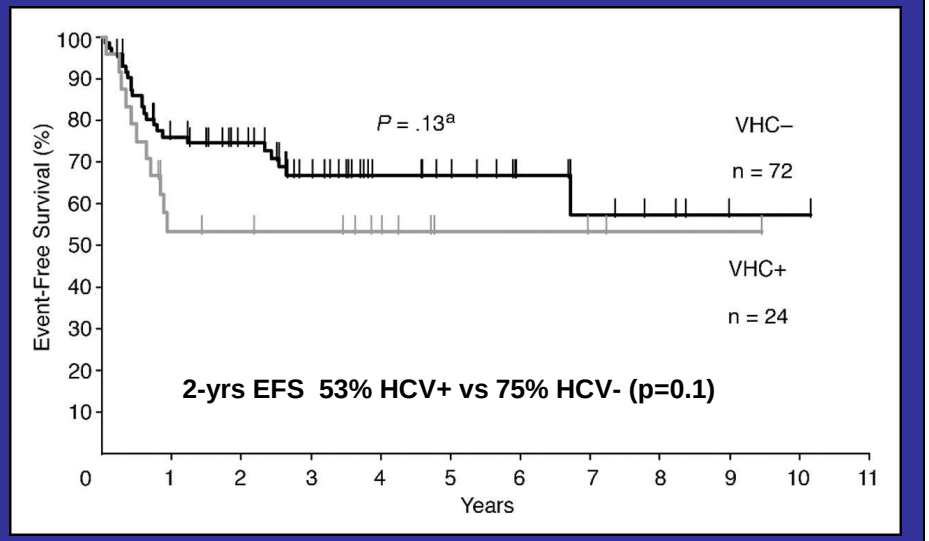
GELA trials LNH93 ed LNH98

- **HCV prevalence** **0,5%** (26/5,586)
- **Histologic shift** **32%** HCV+ *vs* 6% HCV-
- **Spleen involvement** **46%** HCV+ *vs* 17% HCV-
- **Elevated LDH** **77%** HCV+ *vs* 55% HCV-

Besson et al JCO 2006

OS and EFS according to HCV





Besson et al JCO 2006

Liver toxicity

- 65% in HCV+ pts; 30% grade 3-4 in HCV+ pts vs. 1.4% in HCV- pts.
- 30 % modification of protocol in HCV+ pts
- More frequent in later cycles
- I cycle: 25%
- IV cycle: 45%

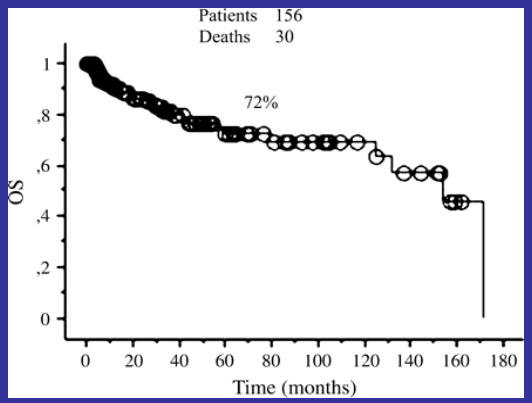
Besson et al JCO 2006

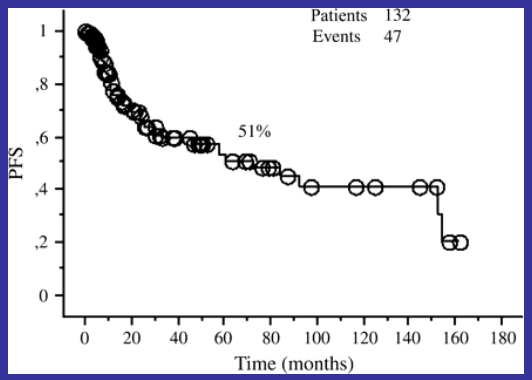
HCV+ DLBCL: an Italian study

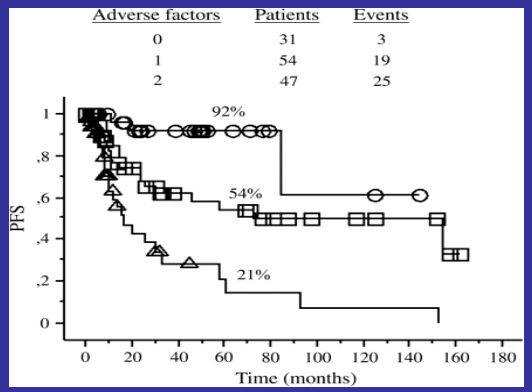
- 156 pts (median age 63 yrs)
- The average prevalence of HCV+ : 16%
- Histologic shift 8%
- Ann Arbor I 20%, II 27%, III 25%, IV 28%
- IPI low 32%, int/low 24%, int/high 28%, high 16%
- Primary extranodal: 43% (skin, liver, stomach)
- Spleen involvement 34%
- Only splenic 19%

Visco et al Ann Oncol 2006

HCV+ DLBCL: an Italian study



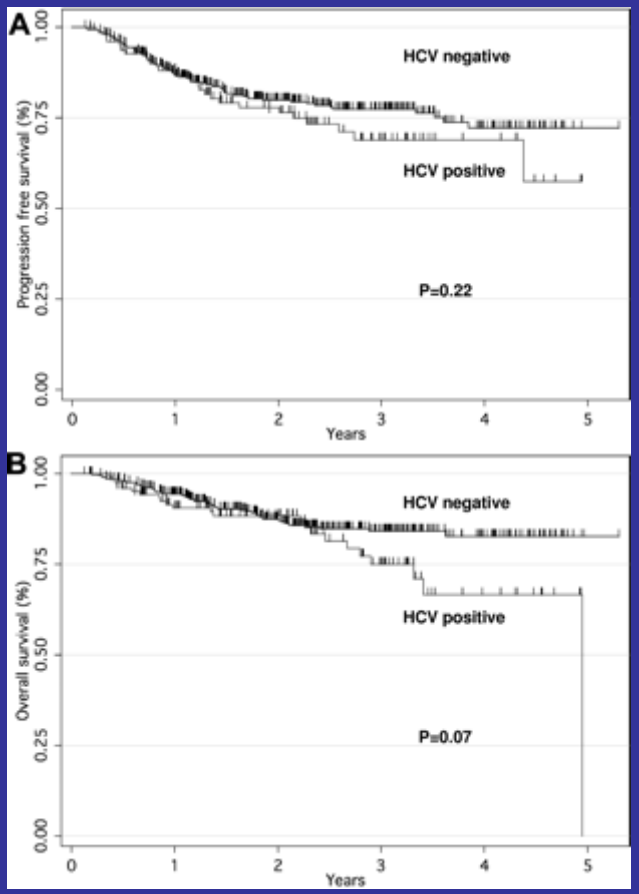




- **85 % antracyclin containing regimens ± Rituximab (27%) ± RT (36%).**
- **85% completed therapy.**
- **Grade III-IV liver toxicity: 4%**
- **No problems with Rituximab**
- **Outcome: CR 67% ; 5-yrs OS 72%; 5-yr FFS 51%.**
- **Risk factors: nodal disease; advanced AAS; HBV coinfection.**

Visco et al Ann Oncol 2006

HCV+ DLBCL and R-CHOP (Japan)



- 553 DLBCL (131 HCV+, 422 HCV-) treated with R-CHOP.
- Clinical characteristics: older; splenic involvement; elevated LDH.
- 3-yr PFS 69% vs 77% (p=0.22); 3-yr OS 75% vs 84% (p=0.07).
- Risk factors: age; advanced AAS
- Severe hepatic toxicity (gr. III-IV): HCV+: 27% vs. HCV-: 3%; Deaths: 5%
- Multiv. analysis: HCV risk factor for severe hepatic toxicity.
- Pretreatment transaminase predictive of severe hepatic toxicity.
- HCV-RNA levels significantly increased during immunochemotherapy.

Severe hepatic toxicity was not associated with poor PFS or OS in HCV+ pts. However, modification of the scheduled dose or chemotherapy withdrawn was required.

Ennishi et al Blood 2011

Conclusioni

- HCV é associato a ~ 10% dei LNH-B.
- Circa il 20% dei linfomi marginali é HCV+.
- **La terapia antivirale sembra essere efficace nei LNH indolenti HCV+.**
- Nei linfomi aggressivi la HCV+ non influenza la prognosi, ma la tossicità epatica severa è più frequente dopo chemioimmunoterapia.
- Se la chemioimmunoterapia abbia un effetto negativo sulla storia naturale della infezione da HCV non è ancora chiarito.
- Il ruolo della terapia antivirale nei linfomi aggressivi rimane indefinito e necessita di studi prospettici .

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