GI Grand Rounds

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October 18, 2007

Case Scenario

- 31 y/o WM with h/o NHL presents to GI clinic directly from Brown Cancer Center for evaluation of elevated LFT's.
- HPI and GI pertinent + symptoms:
  - C/o fluid on abdomen – no prior paracentesis
  - RUQ abdominal pain, worse with stretching or lifting; no change with eating or BM
  - + Jaundice, occasionally
  - + HB 3-4x per week

Case Scenario

Past Medical History:

- Hepatitis C
  - Diagnosed in prison in 2006, No prior Rx
- NHL, Follicular type – Stage IV
  - Diagnosed by LN biopsy 2/05
  - 3 cycles of chemo R-FND 5-7/05, lost to f/u
  - 11/05: Returned to BCC with adenopathy; received cycles 4 and 5 chemo
    - Subsequent Rx held 2/2 Neutropenia

Case Scenario

- NHL, Follicular
  - Spring 2006: Remission with BM biopsy and PET/CT negative
    - Noted elevated LFT's, previously normal 12/05
      - Plan to check HCV status in 4 weeks
  - Spring/Summer 2007: Recurrence
    - Rituxan x 3 in August
  - FLIPI score 3/5

Case Scenario

Social History:

- + Tobacco – 1ppd x 15 yrs, No ETOH/illicits
- + Homemade tattoos – shared needles
- Prison x 8.5 years, recently released
- No prior blood transfusion

Family History:

- Mom – Ovarian CA, Sibs – healthy, No known liver dz

Meds:

- Lasix 80 qd, Spironolactone 200qd, Allopurinol, Urso 500 TID, Relafen, Acyclovir 400 TID, Bactrim DS BID, Phenergan PRN

ROS: essentially negative except HPI and +adenopathy

Case Scenario

- EXAM (pertinent findings):
  - Wt: 255 lbs (116kg)
  - Obese
  - Mildly jaundiced
  - Right cervical LAD
  - Could not appreciate HSM or fluid, and abdomen nontender
  - 2+ pitting edema bilateral lower extremities

Case Scenario

- LABS:
  - CBC: WBC-1.64, Hbg-9.3, Plt-61. MCV-90, RDW-18
  - Coags: PT-15.4, INR-1.6, PTT-37.5
  - Chem: Na-137, K-4.1, Cl-110, CO2-19,
    BUN-11, Cr-0.9
    AST-208, ALT-89, AlkPhos-129, TB-5.1
    TP-5.3, Albumin-2.0
  - HCV Quant: 4.89 million IU
  - HCV Genotype: 1a
  - Ceruloplasmin, ANA, ASMA, Iron studies - Negative

Case Scenario

- Imaging:
  - PET CT (8/1/07):
    - Bilateral LN's neck, increased in size
    - Abdominal mesentery and LN's in upper abdomen, peripancreatic, retroperitoneal c/w recurrent dz
    - Mild splenomegaly
  - RUQ USN (8/17/07):
    - Moderate amount of perihepatic free fluid

Case Scenario

- DDx at initial clinic visit:
  - HCV Cirrhosis
  - Metastatic Follicular Lymphoma
  - Hepatic Lymphoma
  - CASH (chemo-assoc steatohepatitis)

Case Scenario

- Follow-Up:
  - Plan: RTC one week with USN paracentesis and CT scan prior
    - Got lost on the way to ACB
  - F/u 3 weeks later
    - CT scan: no liver or intra-abd malignancy
    - USN: cirrhotic; “not enough fluid to tap”
    - States he saw a Gastroenterologist in Western KY 2 days ago, had blood work drawn, and was told yesterday that his kidneys were not functioning on recent lab work and to hold his diuretics
    - BUN: 40, Creatinine: 2.8 (Baseline: 10/1.0), TB 8.2
    - Admitted pt for acute renal failure

Case Scenario

- Hospital Course:
  - Renal failure – improved rapidly with Albumin
  - Cirrhosis – due to HCV ("If it walks like a duck")-McClain
    - Encephalopathy ensued
      - Infectious w/u negative: Blood, urine cx, CXR
    - Ascites - no SBP
      - USN – portal & hepatic vasc. with normal flow
      - <2g Na+ diet instruction
      - Diuretics restarted after ARF resolved
  - Discharged in stable condition

Case Scenario

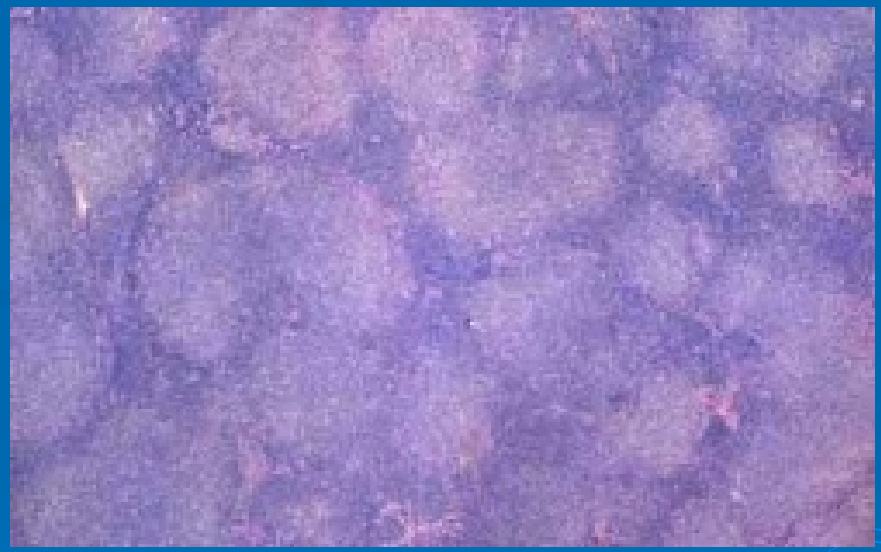
- Hospital Course
  - Transplant discussions:
    - Child Class C Cirrhosis
    - MELD: 22 on date of discharge
      - 31% 90-day mortality due to cirrhosis
  - Would this young, HCV cirrhotic patient with NHL be a transplant candidate?
  - Future Treatment options?

Objectives

- Review Follicular Lymphoma
- Discuss HCV and its role in NHL
- Treatment options for this patient
- Transplant and Malignancy
- Other Lymphomas and Liver (hepatic lymphoma, PTLD)

Follicular Lymphoma

- Prevalence: 22% NHL worldwide, 30% USA
- B Cell Lymphoma
  - Indolent lymphoma
  - Sub-classified into small and large cell disease, and mixture of small/large cells
  - Large Cell Follicular Lymphoma – progresses more rapidly and shorter survival
- Often diffuse disease on presentation



3.1 FLIPI versus WHO/REAL Histological Grade for Identifying Patients at High Risk

Category	Number of patients (%)	Median survival	10-year survival
FLIPI*			
Low risk	128 (49%)	16.5 years	76%
Intermediate risk	76 (29%)	12.4 years	52%
High risk	56 (22%)	5.4 years	24%
Histological grade†			
Grade 1	72 (28%)	25.4 years	62%
Grade 2	102 (39%)	10.3 years	56%
Grade 3a	68 (26%)	18.7 years	60%
Grade 3b	18 (7%)	Not reached	65%

*p-value < 0.0001
†p-value = 0.41

SOURCE: Halaas JL et al. **The Follicular Lymphoma International Prognostic Index (FLIPI) is superior to WHO/REAL histological grade for identifying high-risk patients: A retrospective review of the MSKCC experience in 260 patients with follicular lymphoma.** *Proc ASH* 2004;Abstract 3268.

Characteristic	Prognostic factor (1 point for each)
Age	> 60 years = 1 point
Stage	Stage III or IV = 1 point
Number of lymph node sites involved	> 4 = 1 point
Hemoglobin (Hb) level (red blood cell test)	Blood Hb <12 g/dL = 1 point
Serum LDH level (blood test)	Above the average range = 1 point

FLIPI score: Add poor prognostic factors

Low risk – 0-1 points, Intermediate risk – 2 points

High risk – 3 or more points

Risk Group	5-year Survival Rate	10-year survival rate (ACS website)
low-risk	91%	71%
Intermediate	78%	51%
high-risk	53%	36%

Follicular Lymphoma

- Treatment:
  - Chemotherapy (CVP or CHOP) and radiation: 50-75% achieve complete remission, but may relapse
  - Fludarabine: 1-3% abnl LFT's, <1% liver failure
  - Novantrone: 5-37% abnl LFT's, 3-7% jaundice
  - Rituximab
    - Human/mouse chimeric monoclonal antibody that reacts with CD20 antigen on B cells, inducing cytotoxicity
    - Used in relapsed follicular lymphoma
    - Screen for Hepatitis B in high-risk persons; increased risk reactivation of Hepatitis B

HCV and NHL

- Overview:
  - Initial association found in mixed cryoglobulinemia patients with HCV and NHL
  - Small pilot studies were designed to evaluate an association btw HCV and NHL in pts without cryo
  - Results of studies have differed in terms of the degree of association, the types of lymphomas that develop in HCV pts, and HCV genotype results
  - More recent studies have been large-scale
  - Italy has high prevalence of HCV, so many studies done there

HCV and NHL

- 157 de novo B-NHL subjects (1989-1993) eval'd for HCV
  - Italian, heterosexuals, mean age 65, HIV negative, no h/o IVDA or ETOH, no h/o blood tx
  - HCV ELISA + were confirmed with HCV RNA. Also had liver bx.
- Checked labs for evidence of asymptomatic cryoglobulinemia
- Compared with 143 non-B cell NHL cases at same institution and evaluated for HCV (T-cell, plasma cell, Hodgkin's)
- Follow-up: 72 months

Luppi, M. Clinico-pathological characterization of hepatitis C virus-related B-cell non-Hodgkin's lymphoma without symptomatic cryoglobulinemia. Annals of Oncology, 1998.

HCV and NHL

- Results:
  - 35/157 (22%) B-NHL pts were +HCV vs. with 12/143 (8%) in non-B cell NHL (statistically significant for each different type)
  - No significant difference btw HCV infection and B-NHL subtypes
    - Increased frequency in follicular, marginal zone, and DLBCL
  - No differences in stage, symptoms, or BM involvement btw HCV +/- groups
  - Increased asymptomatic cryoglobulinemia (all types) in HCV+ vs HCV- B-NHL pts ($p<0.0001$)
    - Exclude MC II pts and still have +assoc, p value not given.

Luppi, M. Clinico-pathological characterization of hepatitis C virus-related B-cell non-Hodgkin's lymphoma without symptomatic cryoglobulinemia. Annals of Oncology, 1998.

HCV and NHL

- Median survival time
  - No difference

    HCV+ 48 months

    HCV- 52 months
- Causes of death included lymphoma (equal in HCV +/-) and only 2 HCV + pts died of liver disease

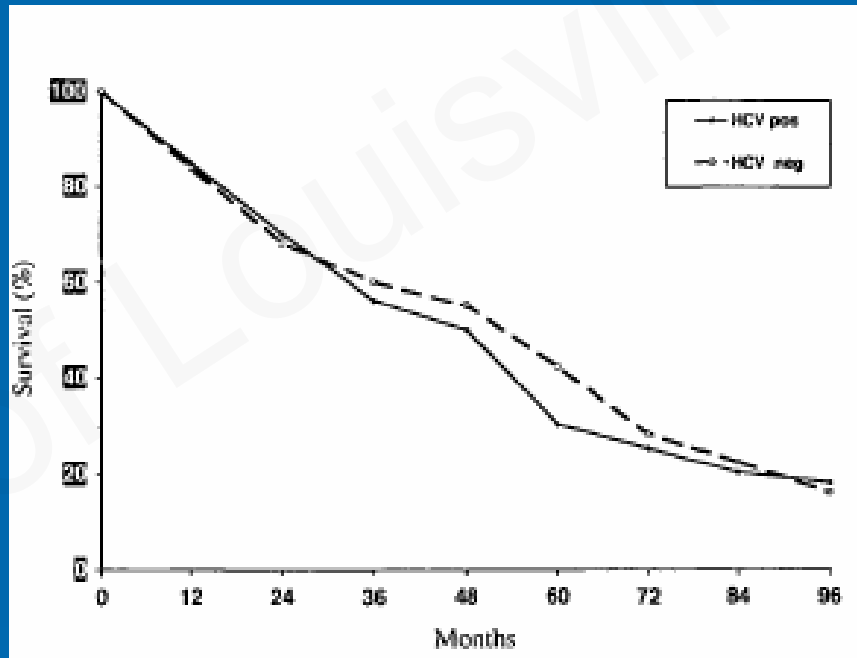


Figure 1. The median survival time in HCV positive and HCV negative B-NHL patients.

Luppi, M. Clinico-pathological characterization of hepatitis C virus-related B-cell non-Hodgkin's lymphoma without symptomatic cryoglobulinemia. Annals of Oncology, 1998.

HCV and NHL

- Retrospective cohort study of 146,394 US Veterans with HCV and matched controls on age, sex, visit dates. 1988-2004.
- HCV + if ICD-9 code. Excluded HIV if Dx before 1st visit.
- Chart review of 100 pts
  - 47/50 in HCV+ group had lab data showing +HCV
  - 5/50 in HCV- group had lab data showing +HCV
- Limitations:
  - 35,696 (6.2%) of "uninfected" HCV pts had HCV
  - 813 pts in HCV+ group and 1539 in HCV- group had HIV
  - Follow-up 2.3 years. Did not exclude cryo (1.5% on NHL cases)

Giordano, TP, et al. Risk of Non-Hodgkin Lymphoma and Lymphoproliferative Precursor Diseases in US Veterans with Hepatitis C Virus. JAMA, May 2007.

HCV and NHL

- HR 1.28 for development of NHL
- 20-30% increased risk for NHL among HCV pts
  - Since used ICD-9 codes to identify NHL, could not distinguish among the subtypes

Table 2. Incidence and Adjusted HRs of Malignancies and Precursor Conditions Among HCV-Infected and HCV-Uninfected Veterans

Outcome	No. of Events (Incidence/100 000 Person-Years)		Comparing HCV-Infected vs HCV-Uninfected Cohorts		
	HCV-Infected Cohort (n = 146 394)	HCV-Uninfected Cohort (n = 572 293)	HR (95% CI)*	Adjusted HR (95% CI)†	*P* Value‡
Malignancies of interest					
Non-Hodgkin lymphoma	319 (114.5)	1040 (95.8)	1.21 (1.07-1.37)	1.28 (1.12-1.45)	<.001§
Waldenström macroglobulinemia	67 (23.9)	98 (8.9)	2.72 (2.00-3.72)	2.76 (2.01-3.79)	<.001§
Hodgkin lymphoma	65 (23.2)	295 (27.0)	0.87 (0.66-1.13)	0.97 (0.74-1.27)	.81
Multiple myeloma	95 (33.9)	431 (39.4)	0.88 (0.70-1.10)	0.95 (0.76-1.19)	.63
Chronic lymphocytic leukemia	69 (24.6)	343 (31.4)	0.81 (0.62-1.04)	0.89 (0.68-1.15)	.37
Acute lymphocytic leukemia	27 (9.6)	184 (16.8)	0.57 (0.38-0.85)	0.75 (0.50-1.13)	.16
Chronic myeloid leukemia	30 (10.7)	163 (14.9)	0.73 (0.49-1.08)	0.84 (0.56-1.24)	.38
Acute nonlymphocytic leukemia	56 (20.0)	243 (22.2)	0.92 (0.68-1.22)	1.04 (0.78-1.40)	.79
Other leukemias	104 (37.1)	479 (43.9)	0.85 (0.69-1.06)	0.96 (0.78-1.19)	.73

Giordano, TP, et al. Risk of Non-Hodgkin Lymphoma and Lymphoproliferative Precursor Diseases in US Veterans with Hepatitis C Virus. JAMA, May 2007.

HCV and NHL

- Large, multi-center case-control study in Europe
  - 5 countries with different prevalence of HCV
- Matched age, sex, center; excluded HIV and organ tx recipients; 1998-2004. 1807 NHL cases, 1788 controls.
  - Included B and non-B cell NHL
- Defined HCV by 3rd gen ELISA testing (sens 98.9%) and performed HCV RNA testing in all ELISA+ subjects
- 2.1% (76) HCV RNA pts developed lymphoma (P=.013)
- Limitations:
  - Did not exclude pts with cryoglobulinemia or Hepatitis B

Nieters, A. Hepatitis C and Risk of Lymphoma: Results of European Multicenter Case-Control Study EPILYMPH. Gastroenterology, 2006;131: 1879-1886.

HCV and NHL

- Elevated OR for lymphoma in relation to HCV RNA was largely explained by the assoc with B-cell lymphoma, but not with T-cell lymphoma or Hodgkin's lymphoma
- HCV assoc with all lymphomas combined, but examined subtypes
  - Strongest assoc with DLBCL; no assoc with Follicular
  - Increased in Genotype 1b HCV subjects

Table 4. OR of Lymphoma Subtypes for HCV Infection

	Anti-HCV+ or HCV RNA+				HCV RNA +			
Lymphoma type[a]	Cases/Controls	OR[b,c]	95% CI	*P* value	Cases/Controls	OR[b,c]	95% CI	*P* value
T-cell lymphoma (n = 101)	2/41	0.88	0.21–3.74	.864	2/29	1.29	0.30–5.55	.37
Hodgkin's lymphoma (n = 239)	3/41	0.97	0.27–3.48	.963	2/29	0.92	0.20–4.30	.915
B-cell lymphoma (n = 1465)	48/41	1.46	0.95–2.24	.086	43/29	1.91	1.18–3.09	.009
DLBCL (n = 392)	18/41	2.19	1.23–3.91	.008	18/29	3.30	1.79–6.11	.0001
FL (n = 210)	2/41	0.50	0.12–2.08	.338	2/29	0.74	0.17–3.15	.679
CLL (n = 342)	10/41	1.16	0.56–2.38	.689	8/29	1.41	0.62–3.17	.410
MM (n = 221)	7/41	1.40	0.61–3.24	.427	5/29	1.57	0.59–4.20	.367
LPL (n = 41)	2/41	1.94	0.43–8.66	.388	2/29	2.97	0.65–13.59	.162
Other B-cell lymphoma (n = 172)	4/41	1.03	0.36–2.93	.959	4/29	1.47	0.50–4.28	.483
Splenic marginal zone lymphoma (n = 35)	1/41	0.83	0.11–6.35	.861	1/29	1.13	0.15–8.72	.907
Other marginal zone lymphoma (n = 77)	3/41	1.76	0.52–5.91	.362	3/29	2.42	0.71–8.28	.160
B-NOS (n = 60)	5/41	4.65	1.66–12.97	.003	4/29	6.88	2.19–21.68	.001

Nieters, A. Hepatitis C and Risk of Lymphoma: Results of European Multicenter Case-Control Study EPILYMPH. Gastroenterology, 2006;131: 1879-1886.

HCV and NHL

- Meta-analysis of studies with control group, >100 cases, excluded HIV
- HCV status defined by 2nd or 3rd generation ELISA
- NHL WHO classification – only major subtypes assessed
- Pooled RR from 18 studies, RR for HCV and NHL: 2.5
  - Follicular Lymphoma, RR 2.7
- Found assoc between HCV and NHL present in similar magnitude in all major NHL subtypes, including Follicular
- No difference between HCV genotypes and risk for NHL

Dal Maso, L. Hepatitis C Virus and Risk of Lymphoma and Other Lymphoid Neoplasms: A Meta-analysis of Epidemiologic Studies. Cancer Epidemiol Biomarkers Prev, 2006.

HCV and NHL

- Proposed pathogenesis
  - Chronic antigenic stimulation leads to B cell proliferation, initially polyclonal, then monoclonal expansion which makes them prone to malignant transformation
  - HCV envelope protein E2 binds to CD81 on B cells and activates intracellular signaling
  - HCV activates nitric oxide synthase → increase NO in B cells. ↑ NO causes DNA breaks and increases mutations

Nieters, A. Hepatitis C and Risk of Lymphoma: Results of European Multicenter Case-Control Study EPILYMPH. Gastroenterology, 2006;131: 1879-1886.

HCV and NHL

- Proposed pathogenesis:
  - Role of BCL-6: gene that encodes transcriptional repressor required for germinal center formation. HCV increases a mutation in BCL-6 which can be found in DLBCL.
  - Possible role of HCV core proteins activating NF-κB pathway, increasing reactive oxygen species
  - Role of TNF-α & IL-10: affect natural clearance HCV and may predispose to DLBCL
  - HCV does not seem to integrate into host genomes
  - HCV does not contain an oncogene

Nieters, A. Hepatitis C and Risk of Lymphoma: Results of European Multicenter Case-Control Study EPILYMPH. Gastroenterology, 2006;131: 1879-1886.

Treatment Options - IFN

- Prospective, Multi-Center Pilot study on effect of antiviral treatment on course of HCV-related B-cell NHL in13 pts.
- Rx: PEG-INTRON 70 mcg qwk & Ribavirin 1200mg qd
  - 60kg or less: 50mcg P-IFN qwk + 1000mg Riba qd. x 6 months
- Monitored HCV RNA q 6 months
- 11/13 completed treatment
  - 7/11 complete response (no evidence for lymphoma)
  - 2/11 partial response (>50% decr LN size)
  - Among these 9/11, 7 had no detectable HCV, 1 had 2log decr
  - The 2 nonresponders had no virologic response to Rx
- Lymphoma response correlated to disappearance of HCV viremia (p=0.005)
- Responders were more likely to be Genotype 2 than Genotype 1 (p=0.035)

Vallisa, D. Role of Anti-Hepatitis C Virus Treatment in HCV-Related, Low-Grade, B-Cell, Non-Hodgkin's Lymphoma: A Multicenter Italian Experience. J of Clin Onco. 2005.

Transplant and Malignancy

- Israel Penn International Transplant Tumor Registry (IPITTR)
  - Registry of >15,000 transplant-related malignancies
  - Consult service for case-by-case assessment of pre-transplant evaluation for pt with h/o cancer
  - For our pt, it was decided that he needed to be in remission for one year before tx consideration
- General Rule:
  - 5 years after cancer “cure” to be transplant candidate

Executive Director
Dr. Joseph Buell

Other Lymphomas and Liver Tx

- Posttransplant Lymphoproliferative Disorders
  - Prevalence: 1% overall
    - 1-2% OLT, 1-3% Renal, 2-6% Cardiac, 2-9% Lung
  - Pathogenesis: Epstein-Barr Virus
    - Immunosuppression impairs EBV-specific T cell-mediated immunity. Loss of these cytotoxic T-cells allows EBV-infected B cells to proliferate.
  - Risk Factors:
    - Degree of immunosuppression, EBV seronegative recipients, prior h/o malignancy pre-transplant, <25 y/o (less likely to have had EBV), fewer HLA matches, first yr s/p Renal Tx

Other Lymphomas and Liver Tx

- PTLD
  - Treatment:
    - Decrease immunosuppression (Tacrolimus)
    - Antivirals – ganciclovir, acyclovir
    - Chemotherapy
    - IV Ig
    - Surgical Resection
    - Radiation
    - IFN-α – antiviral activity (case reports)
  - Prognosis: Worse if in first 6 mos s/p tx, older age, multiple sites. IPI score not helpful.

Other Lymphomas and Liver

- Primary Hepatic Lymphoma
  - Prevalence: 0.4% of primary lymphomas
  - More common with DLBCL
  - Mass on imaging
  - Reports of association with immunosuppression or chronic viral hepatitis

Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed.

Other Lymphomas and Liver

- Metastatic Lymphoma
  - On biopsy, 16% to 26% of patients with NHL are found to have liver infiltration
  - Can have normal or abnormal LFT's
  - Can have extrahepatic biliary obstruction 2/2 nodes in porta hepatis (mimics Cholangio CA)

Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed.

C.A.S.H. (not $$)

- Chemotherapy Associated Steatohepatitis
  - Specific chemotherapy agents increase CASH
    - Irinotecan, oxaliplatin
  - Increased in hepatic involvement of colorectal cancer

Follow up

- 5 days after pt was discharged from JH, he presented to outlying hospital and died within hours.
- Exact details unknown
  - Hypotensive, GI bleeding?
- Would a diagnosis of HCV at time of diagnosis of NHL in this pt have affected outcome?

Summary

- Reviewed Follicular Lymphomas and others
- HCV seems to be an independent risk factor for B-cell NHL
  - Unclear if only for specific subtypes (DLBCL)
- Treatment of HCV improved NHL in small study
- Long-term outcome studies needed
- Should all patients with new diagnosis of NHL be screened for HCV (and HBV)?
  - Would it affect treatment choices and outcomes?