TREATMENT OF HEMOPHILIA
JULY 2011 • NO 52

HCV-RELATED LIVER CANCER IN PEOPLE WITH HAEMOPHILIA

Karina Meijer
Division of Haemostasis and Thrombosis
Department of Haematology
University Medical Centre Groningen
Groningen, The Netherlands

Els B. Haagsma
Department of Gastroenterology and Hepatology
University Medical Centre Groningen
Groningen, The Netherlands

WORLD FEDERATION OF
HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA
Treatment for All

This paper was commissioned by the WFH and originally published by Blackwell Publishing in *Haemophilia*; Epub ahead of print June 9, 2011. DOI: 10.1111/j.1365-2516.2011.02575.x. It is reprinted with their permission.

This publication is accessible from the World Federation of Hemophilia's website at www.wfh.org. Additional copies are also available from the WFH at:

World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel. : (514) 875-7944
Fax : (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

The *Treatment of Hemophilia* series is intended to provide general information on the treatment and management of hemophilia. The World Federation of Hemophilia does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Dose schedules and other treatment regimes are continually revised and new side effects recognized. WFH makes no representation, express or implied, that drug doses or other treatment recommendations in this publication are correct. For these reasons it is strongly recommended that individuals seek the advice of a medical adviser and/or consult printed instructions provided by the pharmaceutical company before administering any of the drugs referred to in this monograph.

Statements and opinions expressed here do not necessarily represent the opinions, policies, or recommendations of the World Federation of Hemophilia, its Executive Committee, or its staff.

Treatment of Hemophilia Monographs
Series Editor
Dr. Johnny Mahlangu

Haemophilia

Haemophilia (2011), 1–8 DOI: 10.1111/j.1365-2516.2011.02575.x

REVIEW ARTICLE

HCV-related liver cancer in people with haemophilia

K. MEIJER* and E. B. HAAGSMA†

**Division of Haemostasis and Thrombosis, Department of Haematology and †Department of Gastroenterology and Hepatology, University Medical Centre Groningen, Groningen, The Netherlands*

Summary. The topic of this monograph is liver cancer associated with chronic HCV infection. We start with some background information on chronic HCV infection and its long-term sequelae, one of which is liver cancer. The rest of the article is concerned with liver cancer or hepatocellular carcinoma (HCC). Epidemiology, risk factors, treatment and outcomes are discussed. We focus on those aspects that are of specific interest in people with haemophilia: studies performed in haemophilia populations, the use of invasive diagnostic and therapeutic tools and the outcome of liver transplantation. Throughout the paper, recommendations are given on surveillance for and diagnosis of HCC and on the practical aspects of invasive procedures. These recommendations are based on professional guidelines, other published evidence and the authors' experience. In general, diagnostic and therapeutic options are the same in persons with and without haemophilia.

Keywords: haemophilia, hepatitis C, hepatocellular carcinoma, liver cancer, liver transplantation

Introduction

Hepatitis C

Hepatitis C is caused by infection with HCV, an RNA flavivirus. In the haemophilia community, HCV was transmitted through clotting factor concentrates. Almost all haemophilia patients who were treated with large-pool coagulation factor concentrates before the mid-1980s, have been infected with HCV. In the majority, this has led to liver disease i.e. chronic hepatitis C.

A discussion of current treatment options for chronic hepatitis C is outside the scope of this monograph. A recent practice guideline can be found at http://www.aasld.org. Although it is commonly stated that haemophilia patients tolerate treatment for chronic hepatitis C less well than other patient groups (e.g., [1]), a recent meta-analysis of studies performed in people with haemophilia concluded that results (rates of sustained response) are similar to those in the general population [2].

Correspondence: K. Meijer, Division of Haemostasis and Thrombosis, Department of Haematology, University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands.
Tel.: +31 50 361 2791; fax: +31 50 361 1790;
e-mail: k.meijer@int.umcg.nl

Accepted after revision 27 April 2011

Cirrhosis

The major complication of chronic hepatitis C is advanced fibrosis and cirrhosis, which develops in 20–30% of patients over 20–30 years [3]. This long time between infection and development of complications means that, although the rate of new hepatitis C infection has sharply declined (to virtually zero in people with haemophilia after the introduction of viral inactivation steps for clotting factor concentrates), the prevalence of cirrhosis caused by chronic hepatitis C is still increasing.

A number of systems are used to grade fibrosis. Most of them score 'no fibrosis' as '0' and 'cirrhosis' as '4'. Advancing grades of fibrosis are scored '1', '2' and '3', but the exact definitions differ in the different systems [4].

The risk of cirrhosis is higher in patients who are older at the time of infection, co-infected with hepatitis B virus or HIV and who are male. Moreover, concomitant other liver disease, obesity, diabetes and alcohol consumption increase the risk of cirrhosis. The rate of development of cirrhosis seems to be lower in African Americans [3].

Haemophilia populations are very informative on the natural history of hepatitis C, because the time of infection is known (the first exposure to large pool concentrates). They confirm that progression to cirrhosis and overt liver disease is more common in patients who were older at the time of infection. A specific problem in haemophilia is co-infection with HIV, which

strongly increases the risk of progression to cirrhosis and development of end stage liver disease. Hazard ratios for progression to end stage liver disease are as high as 8–14 in HIV-positive when compared with HIV-negative patients [5,6].

In HIV-negative patients, the prevalence of symptomatic liver disease was reported to be 3–14% after 16–35 years. The same cohort studies reported liver related death in 0–3% of patients [5–8]. A recent study in a Canadian cohort, using a Markov model incorporating the effect of treatment, predicted that at 20 years after infection, 37% of haemophilia patients would have cirrhosis, 12% hepatocellular carcinoma and 19% would have died from HCV [9]. However, this is probably a major overestimate as in reality most haemophilia patient cohorts have been infected for almost 30 years and have not demonstrated these outcomes.

Although some studies saw more liver disease in patients with more severe bleeding disorders, this was not reported by all. This could be a methodological issue: patients with more severe bleeding disorders often had a longer duration of infection, because they were generally treated and thus infected at an earlier age.

Diagnosis of cirrhosis

The gold standard for the diagnosis of cirrhosis is a liver biopsy, although sampling error is a problem. In haemophilia, there is also the issue of bleeding risk and cost of substitution therapy. Both in persons with haemophilia and others, there is a lot of interest in non-invasive methods to diagnose fibrosis and cirrhosis [10]. Cirrhosis may well be evident on ultrasound (US), if there is irregularity of the liver surface or nodularity of the liver [7], but can be missed. The most well-tested non-invasive options are FibroTest, which is a panel of five biochemical markers and FibroScan which uses transient elastography, an ultrasound-based technique, to measure liver stiffness. In a meta-analysis of diagnostic accuracy (vs. biopsy as the gold standard), the sensitivity of FibroScan was 64% for F2-4 fibrosis and 86% for cirrhosis. For FibroTest, data were difficult to summarize because different cut-off levels were used. If sensitivity above 80% was required, specificity dropped to 40–60% [11]. FibroTest and FibroScan have been tested in haemophilia, but without comparison with liver biopsy [12–14]. When the two tests were compared with each other in haemophilia, concordance was not very good in F2–3 fibrosis, but reasonable (85%) in cirrhosis [12]. Non-invasive tests overcome the issue of bleeding with liver biopsy, but not completely that of costs: FibroTest is only available commercially and cannot be performed in-house and FibroScan requires investment in expensive equipment. The American Association for the Study of Liver Diseases (AASLD) does not recommend the use of the currently available non-invasive tests instead of liver biopsy in routine clinical practice [4].

With the present options for treatment, the main question in clinical practice is whether there are signs of cirrhosis and this question can be answered by a combination of routine liver tests and a routine ultrasound in most patients.

Hepatitis C-related hepatocellular carcinoma

Once patients have developed cirrhosis, they are at risk for liver cancer, i.e. hepatocellular carcinoma (HCC). HCC is the leading cause of death in patients with cirrhosis because of hepatitis C. In the western world, the incidence of HCC is clearly increasing because of chronic hepatitis C. In 2000, 60–70% of HCC in Europe and 50–60% in North America was related to hepatitis C [15]. In other parts of the world, the background incidence of HCC is higher because of chronic hepatitis B and exposure to toxins.

In large studies, the rate of development of HCC was 3–6% per year in patients with HCV cirrhosis. In patients with advanced fibrosis, the rate is approximately half of that [16,17]. In less advanced hepatitis C, the risk of HCC seems very low [17]. An Italian study in persons with haemophilia, performed in the 1990s, reported six cases of HCC in 384 patients with chronic hepatitis C during 4 years of follow-up or 0.4% per year. All cases occurred in the 40 patients who had cirrhosis at baseline [18].

Risk factors

Risk factors for HCC in patients with HCV coincide with the risk factors for progression of HCV chronic hepatitis to cirrhosis. These factors include older age, older age at the time of acquisition of infection, male gender, heavy alcohol intake, co infection with HBV or HIV, a transfusion-related mode of HCV acquisition and possibly diabetes and obesity [19]. A recent meta-analysis showed that infection with genotype 1b may also be associated with an increased risk of HCC (relative risk of 1.78) [20].

Strategies for early detection

Patients with an increased risk of HCC are candidates for surveillance: periodic examinations [most often US or alpha fetoprotein (AFP)] to look for early, asymptomatic HCC. The rationale behind surveillance is that early HCC can often be treated, whereas advanced, symptomatic HCC has a very poor prognosis. Surveillance has become routine practice, although scientific evidence for its benefit is scarce. A number of uncontrolled cohort studies in cirrhosis (not specifically

hepatitis C) showed improved survival [21,22]. Only one randomized controlled trial has been performed, in hepatitis B. In that study, HCC related mortality was reduced by 37% (83 vs. 132/100 000), using US and AFP [23]. The main problem with uncontrolled studies of surveillance is lead time bias: the earlier a tumour is found, the longer survival seems, simply because we start counting at an earlier time point. Moreover, it is not known if all small HCC progress to clinical disease. Thirdly, the usefulness of early diagnosis is limited in patients with advanced liver disease or co-morbidity, who might not be candidates for curative treatment (as discussed below).

The AASLD guidelines recommend surveillance in all patients with hepatitis C in whom the annual risk of HCC exceeds 1.5%. This threshold is based on cost effectiveness analyses [24,25]. With an annual risk of 3–6%, surveillance is recommended in all patients with hepatitis C cirrhosis. No clear recommendations were given in patients with late stage (F3) fibrosis, although literature indicates that HCC risk is not negligible. It seems to be at least half of that in cirrhosis [16,17], which would cross the threshold of 1.5% per year. In patients with F1 (mild) or F2 (moderate) fibrosis, the risk of HCC is probably much lower.

The risk of HCC decreases in patients with cirrhosis who are treated with interferon-based therapies, most strongly when there is a sustained virological response. A recent meta-analysis reported a relative risk of 0.43 in treated patients when compared with untreated controls, and 0.35 in patients with a sustained response when compared with treated patients without response [26]. However, the remaining absolute risk is still not completely clear and AASLD recommends ongoing surveillance in those patients. Surveillance is not required in patients who had not developed cirrhosis at the time of successful HCV treatment. Ultrasonography of the liver is the best available tool for surveillance for HCC, although sensitivity and specificity are limited at 65–80% and 90% respectively. Other limitations of the technique are operator dependency, decreased quality in obese patients and decreased sensitivity in patients with cirrhosis. Periodic measurement of serum AFP is only recommended if ultrasonography is not available: there is no single cut-off level that is both sensitive and specific enough for the presence of HCC. However, because of the limitations of US, many clinicians still favour the combination of US and AFP. A sudden rise of AFP and/or a high level of AFP deserves further radiological diagnostics (4-phase CT scanning) in case US is not conclusive.

The interval between ultrasounds is determined by the growth rate of the tumour: the aim is to diagnose HCC between its earliest visibility on US and the time it has reached 2 cm in diameter. From biological studies, this window is 6–12 months. Most clinical evidence does not show added benefit for surveillance intervals of 6 months over 12 months and AASLD's recommendation to screen at 6 months' interval is based on data in hepatitis B.

Evidence in haemophilia. Santagostino *et al.* performed a non-randomized, two-arm study in persons with haemophilia, in which they compared surveillance intervals of 6 and 12 months [27]. They used both US and AFP. More cases of HCC were diagnosed in the 6-month group (0.40% vs. 0.14% per year), but in both groups tumours were multinodular and long-term survival was only seen in patients who had undergone orthotopic liver transplantation (OLT). Too few HCC were diagnosed for a meaningful comparison of the two strategies: in the 12-month group, two patients died and one was a long-term survivor; in the 6-month group, one patient was recently diagnosed, one died, one was on the waiting list for OLT and two were long-term survivors. The Santagostino study was designed after an earlier cohort study by the same group tested annual screening with US and AFP [18]. In this study, all HCC were late stage disease without options for curative treatment. It should of course be noted that treatment options have increased after these two studies were performed.

Recommendation. We perform yearly US combined with twice-yearly AFP measurement in all haemophilia patients with chronic hepatitis C, including those in whom cirrhosis has not been diagnosed. We do this because fibrosis without cirrhosis is also associated with HCC and because present diagnostic methods (including non-invasive tests) cannot reliably exclude cirrhosis. We also continue surveillance in patients who have successfully been treated for HCV, as we did not exclude cirrhosis in most of them before treatment.

Diagnosis

We discuss here the diagnosis of HCC in the setting of patients who have an a priori high risk of HCC: patients with cirrhosis due to hepatitis C. Strategies are different when HCC suspected in a patient with an a priori low risk, this is outside the scope of this monograph.

The diagnosis of HCC is different from most other cancers, as histology is not required if risk factors (i.e., cirrhosis) are present and imaging is typical. HCC exclusively receives arterial blood supply through the arterial tumour vessels, and accordingly most HCCs are hypervascular on angiography and as seen in the arterial phase of contrast-enhanced imaging. However, this hypervascularity is not present in dysplastic nodules, and in the majority of cases also absent in early well-differentiated HCC. It follows that the diagnosis of HCC in a cirrhotic liver can be reliably made when contrast-enhanced CT or MRI show enhancement of a nodule in the arterial phase and less enhancement in the venous phase (relative to the surrounding liver tissue).

When compared with the gold standards of histological examination of an explanted/resected liver, biopsy or follow-up, CT had a sensitivity of 68% and specificity of 93%. In the same meta-analysis, MRI had a sensitivity of 81% and specificity of 85% [28]. Ultrasonography, which is most valuable in surveillance, is not sufficiently specific for diagnosis. A high level of AFP (e.g. >500 U L^{-1}) may help in establishing the diagnosis; however, the level is often only slightly raised which does not discriminate between tumour and active hepatitis. The role of FDG-PET scanning is limited in initial diagnosis as only about half of tumours are positive. However, FDG-PET might be useful in staging the disease [29].

The aim of surveillance programmes as discussed above is to diagnose HCC in a stage that curative treatment can be offered. If symptoms occur, HCC is most often in an advanced stage. Such patients present with decompensation of previous compensated liver disease, pain, weight loss or an upper abdominal mass or with metastases in intra-abdominal lymph nodes, lung, bone and adrenal glands [30].

The diagnostic approach to a suspected HCC depends on the size of the lesion. Lesions smaller than 1 cm are usually not malignant. Small nodules comprise a broad range of entities, some benign, some with malignant potential, some clearly malignant. Careful study of pathological and clinical features of small nodular lesions in cirrhotic liver has shown the evolution from premalignant lesions (low and high grade dysplastic nodules) to early, well-differentiated HCC to moderately differentiated HCC [31]. AASLD recommends that nodules smaller than 1 cm should be followed-up by ultrasound, at 3–6 months intervals. If they remain stable for 2 years, standard surveillance can be resumed.

The AASLD recommendations are more complicated for lesions larger than 1 cm. For these, either contrast enhanced CT or MRI is advised. If the image is typical, HCC is diagnosed. If it is not, the other modality is also used. If this results in a typical image, HCC is diagnosed. If this is also inconclusive, biopsy is needed. This approach has been validated by a number of studies. The main limitation is that 30–40% of HCC is missed on fine needle biopsy [32]. Repeated biopsies are often necessary. Other problems of biopsy include the risk of needle track seeding (2.7% in a recent meta-analysis [33]) and the difficulty to differentiate HCC from high-grade dysplastic nodules on small biopsy samples. In persons with haemophilia, the risk of bleeding and requirement of coagulation factor concentrates need to be considered [34].

The most widely used staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) staging scheme (Table 1) [35].

Recommendation. We follow the AASLD recommendations for diagnosis. The diagnostic work-up and indications for biopsy are not different from those in patients without haemophilia.

Table 1. The Barcelona Clinic Liver Cancer (BCLC) staging system (35).

	HCC	Child-Pugh	WHO performance status (63)
O, very early stage	Single, <2 cm	–	0
A, early stage	Single or max 3 nodules <3 cm	A, B	0
B, intermediate stage	Multinodular	A, B	0
C, advanced stage	Portal invasion, N1, M1	A, B	1–2
D, end stage		C	>2

HCC, hepatocellular carcinoma.

Treatment of HCC

Removal of the tumour(s), prior to spreading outside the liver is the only option for cure. This can be achieved by surgical resection, local ablation or liver transplantation. The first two can only be considered in selected cases with one or two nodules and relative adequate function of the cirrhotic liver. Impaired liver function and regenerative capacity in combination with the precancerous condition of the liver make the outcome less than optimal.

Liver transplantation is in itself the best option as it both cures the cirrhosis and removes both malignant and premalignant lesions. However, patient characteristics, donor shortage and (potential) tumour spread outside the liver may preclude this option. If local ablation or resection are not feasible, most liver transplant centres only accept patients for liver transplantation if the tumour load is not outside the so-called Milan criteria: one solitary HCC lesion ≤5 cm or maximum three lesions ≤3 cm, no gross vascular invasion and no regional node or distant metastases [36].

The different treatment modalities are discussed in more detail below.

Resection

Only a small minority of patients with HCC in the setting of HCV infection are good candidates for resection, because most will have cirrhosis and liver dysfunction. Patients with cirrhosis but still well-preserved liver function can be eligible, if their bilirubin and portal blood pressure are normal. In that case, 5-year survival can exceed 70%, while in less rigorously selected patients, 5-year survival is about 50% [37].

Recurrence of HCC, either a true recurrence of the same tumour or *de novo* HCC, is eventually seen in up to 70% of patients who undergo resection. Adjuvant therapy, either before or after surgery, does not reduce this rate [38]. Data on the treatment of recurrence are

scarce, although liver transplantation might be an option in some patients.

Evidence in haemophilia. In persons with haemophilia, only a few cases of partial hepatectomy have been described, including one in a patient with an inhibitor to factor VIII (FVIII) [39–41]. No complications were reported.

Practical recommendations for partial hepatectomy. Before surgery, the presence of an inhibitor to FVIII or FIX should be excluded. Throughout surgery, substitution is aimed at FVIII or FIX levels between 80 and 100%. We use continuous infusion in the postoperative period, aiming at levels between 50 and 80% in the first 5 days. After that, we either continue continuous infusion with levels between 30 and 50% until 2 weeks postoperatively, or we switch to bolus injections with trough levels of 30%. We prefer continuous infusion for as long as patients are hospitalized, especially on surgical wards where nurses are not used to work with coagulation factor concentrates. Unless there are contraindications (i.e., arterial disease or otherwise increased risk of thrombosis), we also use tranexamic acid (1 g trice daily) for the first 7 days. We start low molecular weight heparin for thromboprophylaxis on the first day after surgery, if there have been no bleeding complications and continue as long as factor levels are above 50%. Compression stockings worn during surgery and until the patient has completely mobilized.

Local ablation

Percutaneous ablation is a curative option for patients with small HCC who cannot undergo resection. It is also used in patients on the waiting list for liver transplantation. Tumours are injected with a chemical substance (most often ethanol) or with a transducer that either heats (radiofrequency ablation, RFA) or freezes the malignant cells. Most centres routinely use percutaneous ethanol injection (PEI) and/or RFA [42].

For PEI, multiple sessions of injections are often required to achieve maximal control of the HCC, and it performs less well in larger tumours. By contrast, RFA is effective in larger tumours, but has a higher rate of complications (including bleeding) and is more expensive [42].

A number of studies have compared PEI and RFA. A recent meta-analysis summarized the evidence as follows: in HCC <2 cm, there is no significant difference in survival using both methods. In larger HCC, RFA has lower recurrence rates and better survival [43]. Likewise, the AASLD recommends RFA over PEI in tumours >2 cm.

Debate is ongoing whether RFA might even be noninferior to resection in patients with HCC <2 or 3 cm [44,45]. In Western countries, resection is still the first option, although in Japan RFA may be offered as first choice.

Evidence in haemophilia. Published data on percutaneous ablation in persons with haemophilia are limited to a series of five PEIs. Before the procedure, coagulation factor concentrates were administered to achieve levels of 65–100% FVIII or FIX. After the procedure, levels >40% were maintained for another 2 days. There were no early complications, but one patient presented with gastrointestinal bleeding on day 4, for which no source was found [46].

Practical recommendations for percutaneous ablation. Our practice is to aim for 80–100% of FVIII/FIX during the procedure, and afterwards keep levels above 50% for 3 days and above 30% for another 2 days.

Liver transplantation

Liver transplantation in haemophilia has the added bonus of, in addition to potentially cure the HCC and cirrhosis, curing the coagulation defect. However, the indications for liver transplantation are exactly the same in persons with haemophilia as in others, including the above mentioned Milan criteria for acceptable tumour load. In the study that introduced these criteria, survival was 75% at 4 years [36]. In a large multi-centre retrospective review, patients who satisfied the Milano criteria had a 5-year survival of 73%, compared to 54% in those who had larger tumours or macrovascular invasion [47].

In liver transplantation, the question is not just what the optimal treatment for an individual patient is. Given the scarcity of donor organs, the optimal use of available cadaveric livers must also be considered. To achieve fair allocation, livers are allocated based on objective criteria (serum bilirubin, serum creatinin, INR), which are combined in the Model for End-Stage Liver Disease (MELD) score [48]. The MELD score is not easily calculated, as it uses logarithms, but calculators are available online (for instance on the United Network for Organ Sharing website, http://www.unos.org). After some discussion on the relative weight of HCC, patients are now given 22 MELD points. The waiting time for transplantation is considerable, depending on blood group, local waiting list and local availability of organs. A proportion of patients has progression of HCC or dies while on the waiting list. This has prompted the use of living donor transplantation. In this procedure, the right hepatic lobe of a healthy volunteer donor (close family member or spouse) is used [49]. The advantages of a living donor are a shorter waiting period and elective surgery. A modelling study showed that a living transplantation increases life expectancy and cost-effectiveness when compared with cadaveric transplantation, as soon as the waiting time for a cadaveric transplant exceeds 7 months

[50]. There is one major downside: the risk to the donor. Estimated risk of complications is 20–40% and mortality is 0.3–0.5% [49].

Evidence in haemophilia. The first successful liver transplantation in haemophilia was performed in 1985 [51]. The Birmingham haemophilia and liver centres reported a series of 11 liver transplants in haemophilia patients between 1990 and 2001. Five-year survival was nine of 11 (82%). Data on HCV recurrence were available in eight. Two developed cirrhosis at 1 and 3 years post-transplantation respectively. Four others had histological evidence of HCV hepatitis. Coagulation factor substitution was managed by continuous infusion and could be stopped at a median of 36 h after transplantation [52]. Transplantation has also been performed in patients with inhibitors to FVIII [53]. In 2005, the first case of living donor transplantation was reported in haemophilia [54].

Liver transplantation has now become standard practice in persons with haemophilia who have an indication for this procedure. This requires close collaboration between liver surgeon, hepatologist, anaesthesiologist and haematologist.

Practical recommendations for liver transplantation: In our centre, we formulate a plan for factor substitution before patients are placed on the waiting list. This plan is available to all team members, in the electronic patient file. An inhibitor is excluded at this time point, with repeat measurements at least every 6 months (in low risk patients with generally >1000 exposure days). Shortly before transplantation, FVIII or FIX concentrate is infused, aiming for levels of 100 and 80% respectively. After this initial bolus, a continuous infusion of 4 units per kg bodyweight per hour is started. A FVIII or FIX level is measured before the start of surgery. During transplantation, laboratory staff is available for repeat measures if surgery is complicated or haemostasis is insufficient. At the end of surgery and at least daily afterwards, factor levels are again monitored. Decrease of substitution is guided by these measurements.

Palliative options

Palliative options with proven efficacy (increased survival) are limited to trans-catheter arterial chemoembolization (TACE) and sorafenib. The AASLD recommends TACE in BCLC intermediate (B) stage HCC, and sorafenib in advanced (C) stage.

In TACE, chemotherapy (either doxorubicin or cisplatin in lipiodol emulsion) is infused directly in the hepatic artery. Subsequently, the blood vessel is embolized using small particles, thus combining cytotoxic and ischaemic damage to the tumour. A recent advance is combining both steps in the use of embolic particles that elute cytotoxic drugs [42].

Extensive tumour necrosis is seen after TACE in most patients, with objective responses in 20–60% and very rare complete responses. Necrosis causes fever, abdominal pain and ileus, from which patients normally recover in 2 days. TACE has been shown to improve survival, but the size of the gain depends heavily on patient characteristics. In patients with more advanced disease (i.e., BCLC stage C, especially those with portal invasion) the benefits do not outweigh the risk of complications [42].

Evidence in haemophilia. Four cases of TACE in persons with haemophilia have been described in the same paper quoted earlier for PEI [46]. Here too, substitution was used for 2 days after the procedure. Moreover, no early complications were seen but 2/4 patients had late gastrointestinal bleeding.

We have used TACE twice, in a single patient with severe haemophilia A who had a longstanding inhibitor. He was treated with recombinant factor VIIa, 90 $\mu g\ kg^{-1}$, for 3 days. During the procedure and the first 12 h afterwards, dosing was every 2 h. Afterwards, we decreased the interval between doses. The procedure was uncomplicated.

In advanced HCC (BCLC grade C), sorafenib offers a survival advantage of about 3 months [55,56], but little effect on time to symptomatic progression. Sorafenib is a multikinase inhibitor that inhibits, among others, the vascular and platelet-derived growth factors. It is taken orally twice daily. The main side-effects are a skin hand-foot syndrome and diarrhoea.

Other therapies

No other therapies than those discussed above have proven efficacy in HCC. Quite some studies have dealt with the use of Chinese herbal medicine, mostly as an adjunct to other therapies [57]. Most of these studies have found a positive effect, but the quality of the evidence is generally low and these drugs are not used in main-stream medicine. A fair number of good quality trials have tested tamoxifen. A meta-analysis concluded that it has no effect survival [58].

The choice of treatment modality for HCC is not influenced by the presence of haemophilia. However, many options are invasive and require the expertise of a Haemophilia Treatment Centre.

Prognosis. Patients with early stage HCC (BCLC stage 0 and A) who can be treated with curative intent (resection, liver transplantation or ablation) can expect a 5-year survival of 50–70% [59].

Although transplantation cures the underlying cirrhosis, it does not cure HCV. So far, there are no successful strategies to prevent recurrent HCV infection after transplantation. In most patients, HCV recurs in

the transplanted liver, with a faster development of fibrosis and cirrhosis than in a native liver [60]. Current practice is to start a course with pegylated-interferon plus ribavirin when significant fibrosis has developed [4]. Once cirrhosis post-transplant develops, mortality is high (26% after 1 year in a study in 39 patients [61].

There are no surveillance guidelines for recurrent HCC after transplantation. In our centre, we perform twice yearly ultrasound, AFP measurement and chest X-ray. The utility of this follow-up is probably limited, because there are few therapeutic options for recurrent or metastatic HCC.

For patients who are treated palliatively (TACE or sorafenib), 3-year survival is 10–40% [59]. Patients who were candidates for palliative treatment, but did not receive it (the control arm in RCTs) had 1- and 2-year survivals of 18 and 7% respectively [62]. Median survival of patients with advanced HCC, with only symptomatic treatment, is <3 months [59].

Acknowledgement

This paper was originally commissioned by the World Federation of Hemophilia and will also be published in their Treatment of Hemophilia monograph series.

Authors' contributions

Dr. Meijer wrote the paper and Dr. Haagsma revised the paper.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

1 Nash KL, Bentley I, Hirschfield GM. Managing hepatitis C virus infection. *BMJ* 2009; **338**: b2366.

2 Franchini M, Mengoli C, Veneri D, Mazzi R, Lippi G, Cruciani M. Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis. *J Antimicrob Chemother* 2008; **61**: 1191–200.

3 Seeff LB. The history of the "natural history" of hepatitis C (1968–2009). *Liver Int* 2009; **29**(Suppl. 1): 89–99.

4 Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335–74.

5 Goedert JJ, Eyster ME, Lederman MM *et al.* End-stage liver disease in persons with hemophilia and transfusion-associated infections. *Blood* 2002; **100**: 1584–9.

6 Posthouwer D, Markis M, Yee TT *et al.* Progression to end-stage liver disease in patients with inherited bleeding disorders and hepatitis D: an international, multicenter cohort study. *Blood* 2007; **109**: 3667–71.

7 Meijer K, Haagsma EB, Kok T, Schirm J, Smid WM, van der Meer J. Natural history of hepatitis C in HIV-negative patients with congenital coagulation disorders. *J Hepatol* 1999; **31**: 400–6.

8 Franchini M, Rossetti G, Tagliaferri A *et al.* The natural history of chronic hepatitis C in a cohort of HIV-negative Italian patients with hereditary bleeding disorders. *Blood* 2001; **98**: 1836–41.

9 Thein HH, Yi Q, Heathcote EJ, Krahn MD. Prognosis of hepatitis C virus-infected Canadian post-transfusion compensation claimant cohort. *J Viral Hepat* 2009; **16**: 802–13.

10 Smith JO, Sterling RK. Systematic review: non-invasive methods of fibrosis analysis in chronic hepatitis C. *Aliment Pharmacol Ther* 2009; **30**: 557–76.

11 Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. *Am J Gastroenterol* 2007; **102**: 2589–600.

12 Maor Y, Halfon P, Bashari D *et al.* Fibrotest or Fibroscan for evaluation of liver fibrosis in haemophilia patients infected with hepatitis C. *Haemophilia* 2010; **16**: 148–54.

13 Kitson M, Roberts S, Kemp W *et al.* The prevalence of significant liver fibrosis and cirrhosis in haemophilia patients infected with hepatitis C using FibroScan. *Haemophilia* 2011; **17**: 316–7.

14 Posthouwer D, Mauser-Bunschoten EP, Fischer K, Van Erpecum KJ, De Knegt RJ. Significant liver damage in patients with bleeding disorders and chronic hepatitis C: non-invasive assessment of liver fibrosis using transient elastography. *J Thromb Haemost* 2007; **5**: 25–30.

15 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907–17.

16 Lok AS, Seeff LB, Morgan TR *et al.* Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology* 2009; **136**: 138–48.

17 Yoshida H, Shiratori Y, Moriyama M *et al.* Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of hepatocarcinogenesis by interferon therapy. *Ann Intern Med* 1999; **131**: 174–81.

18 Tradati F, Colombo M, Mannucci PM *et al.* A prospective multicenter study of hepatocellular carcinoma in italian hemophiliacs with chronic hepatitis C. The Study Group of the Association of Italian Hemophilia Centers. *Blood* 1998; **91**: 1173–7.

19 El Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. *Hepatology* 2002; **36**: S74–S83.

20 Raimondi S, Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *J Hepatol* 2009; **50**: 1142–54.

21 Sangiovanni A, Del Ninno E, Fasani P *et al.* Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. *Gastroenterology* 2004; **126**: 1005–14.

22 Wong GL, Wong VW, Tan GM *et al.* Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. *Liver Int* 2008; **28**: 79–87.

23 Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; **130**: 417–22.

24 Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. *Am J Gastroenterol* 2003; **98**: 679–90.

25 Bolondi L, Sofia S, Siringo S *et al.* Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut* 2001; **48**: 251–9.

26 Singal AK, Singh A, Jaganmohan S *et al.* Antiviral therapy reduces risk of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *Clin Gastroenterol Hepatol* 2010; **8**: 192–9.

27 Santagostino E, Colombo M, Rivi M *et al.* A 6-month versus a 12-month surveillance for hepatocellular carcinoma in 559 hemophiliacs infected with the hepatitis C virus. *Blood* 2003; **102**: 78–82.

28 Colli A, Fraquelli M, Casazza G *et al.* Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. *Am J Gastroenterol* 2006; **101**: 513–23.

29 Khan MA, Combs CS, Brunt EM *et al.* Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. *J Hepatol* 2000; **32**: 792–7.

30 Yuki K, Hirohashi S, Sakamoto M, Kanai T, Shimosato Y. Growth and spread of hepatocellular carcinoma. A review of 240 consecutive autopsy cases. *Cancer* 1990; **66**: 2174–9.

31 International Consensus Group for Hepatocellular Neoplasia. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. *Hepatology* 2009; **49**: 658–64.

32 Durand F, Regimbeau JM, Belghiti J *et al.* Assessment of the benefits and risks of percutaneous biopsy before surgical resection of hepatocellular carcinoma. *J Hepatol* 2001; **35**: 254–8.

33 Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. *Gut* 2008; **57**: 1592–6.

34 Kessler CM. Update on liver disease in hemophilia patients. *Semin Hematol* 2006; **43**: S13–S17.

35 Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329–38.

36 Mazzaferro V, Regalia E, Doci R *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693–9.

37 Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; **30**: 1434–40.

38 Schwartz JD, Schwartz M, Mandeli J, Sung M. Neoadjuvant and adjuvant therapy for resectable hepatocellular carcinoma: review of the randomised clinical trials. *Lancet Oncol* 2002; **3**: 593–603.

39 Shen SC, Harada A, Kurokawa T *et al.* Partial hepatectomy for hepatocellular carcinoma in a patient with hemophilia: a case report. *Hepatogastroenterology* 1994; **41**: 283–6.

40 Narushima Y, Ishiyama S, Kawashima K, Shimamura H, Yamaki T, Yamauchi H. Operated hepatocellular carcinoma in two HIV- and HCV-positive hemophilic patients. *J Hepatobiliary Pancreat Surg* 2004; **11**: 207–10.

41 Jones AE, Roy A, Armstrong T, Rees M, Welsh FK. Successful liver surgery in a haemophilia patient with high titre factor VIII inhibitor. *Haemophilia* 2009; **15**: 1332–3.

42 Lencioni R. Loco-regional treatment of hepatocellular carcinoma. *Hepatology* 2010; **52**: 762–73.

43 Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgro G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular carcinoma: a meta-analysis. *J Hepatol* 2010; **52**: 380–8.

44 Livraghi T, Meloni F, Di Stasi M *et al.* Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology* 2008; **47**: 82–9.

45 Zhou Y, Zhao Y, Li B *et al.* Meta-analysis of radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma. *BMC Gastroenterol* 2010; **10**: 78.

46 Toyoda H, Fukuda Y, Yokozaki S, Hayashi K, Saito H, Takamatsu J. Safety and complications of interventional radiology for hepatocellular carcinoma in patients with haemophilia and cirrhosis. *Br J Haematol* 2001; **112**: 1071–3.

47 Mazzaferro V, Llovet JM, Miceli R *et al.* Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35–43.

48 Freeman RB Jr, Wiesner RH, Harper A *et al.* The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl* 2002; **8**: 851–8.

49 Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med* 2002; **346**: 1074–82.

50 Sarasin FP, Majno PE, Llovet JM, Bruix J, Mentha G, Hadengue A. Living donor liver transplantation for early hepatocellular carcinoma: a life-expectancy and cost-effectiveness perspective. *Hepatology* 2001; **33**: 1073–9.

51 Bontempo FA, Lewis JH, Gorenc TJ *et al.* Liver transplantation in hemophilia A. *Blood* 1987; **69**: 1721–4.

52 Wilde J, Teixeira P, Bramhall SR, Gunson B, Mutimer D, Mirza DF. Liver transplantation in haemophilia. *Br J Haematol* 2002; **117**: 952–6.

53 Dzik WH, Laposata M, Hertl M, Sandberg WS, Chatterji M, Misdraji J. Case records of the Massachusetts General Hospital. Case 38-2008. A 58-year-old man with hemophilia, hepatocellular carcinoma, and intractable bleeding. *N Engl J Med* 2008; **359**: 2587–97.

54 Au WY, Liu CL, Lo CM, Fan ST, Lam CK. Living donor liver transplantation for hepatitis C related hepatocellular carcinoma in a haemophilia A patient. *Haemophilia* 2005; **11**: 405–7.

55 Llovet JM, Ricci S, Mazzaferro V *et al.* Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378–90.

56 Zhang T, Ding X, Wei D *et al.* Sorafenib improves the survival of patients with advanced hepatocellular carcinoma: a meta-analysis of randomized trials. *Anticancer Drugs* 2010; **21**: 326–32.

57 Cho WC, Chen HY. Transcatheter arterial chemoembolization combined with or without Chinese herbal therapy for hepatocellular carcinoma: meta-analysis. *Expert Opin Investig Drugs* 2009; **18**: 617–35.

58 Nowak AK, Stockler MR, Chow PK, Findlay M. Use of tamoxifen in advanced-stage hepatocellular carcinoma. A systematic review. *Cancer* 2005; **103**: 1408–14.

59 Bruix J, Llovet JM. Major achievements in hepatocellular carcinoma. *Lancet* 2009; **373**: 614–6.

60 Yilmaz N, Shiffman ML, Stravitz RT *et al.* A prospective evaluation of fibrosis progression in patients with recurrent hepatitis C virus following liver transplantation. *Liver Transpl* 2007; **13**: 975–83.

61 Berenguer M, Prieto M, Rayon JM *et al.* Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. *Hepatology* 2000; **32**: 852–8.

62 Cabibbo G, Enea M, Attanasio M, Bruix J, Craxi A, Camma C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. *Hepatology* 2010; **51**: 1274–83.

63 Oken MM, Creech RH, Tormey DC *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55.

WORLD FEDERATION OF
HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA
Treatment for All

1425 René Lévesque Blvd. W., Suite 1010 Montréal, Québec H3G 1T7 CANADA
Tel.: +1 (514) 875-7944 Fax: +1 (514) 875-8916
www.wfh.org