Non-surgical treatment of hepatocellular carcinoma (HCC)

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Introduction

World-wide, HCC is detected in 250.000 new cases per year. It is expected that the incidence will rise in Europe and the USA as a consequence of the progression of HCV-induced cirrhosis (1). Indeed, in Western areas, more than 85% of HCC develop in patients with pre-existing cirrhosis. Nevertheless, the cases with HCC without cirrhosis are equally important to study. We compared the characteristics of 56 patients with HCC but without cirrhosis with those of 84 cases with cirrhosis (2). The non-cirrhotic cases were younger (50 ± 19 yrs vs 62 ± 10), had a M to F ratio of 1.6 to 1 (vs 4.7 to 1 in cirrhotics), had near-normal AST levels (40 ± 5vs 79 ± 8), a comparable a-foetoprotein (AFP) and ferritin increase, but a lower incidence of previous HBV contact (18% vs 52%), and less aHCV (13% vs 40%). In the non-cirrhotic group, tumour size was larger (> 10 cm in 44% vs 14%), it was more often monofocal (76% vs 52%) and the location was 33% in the left lobe (vs 10%). The prime treatment is resection, but other modalities (see further) might be required if the tumour is not anymore resectable. "Why do these young patients develop HCC ?" remains a burning question. Is there a genetic predisposition, an environmental cause or are there combinations of factors ?

Since the majority of patients with HCC have underlying cirrhosis, the first approach is to prevent HCC by interfering with the evolution in and of the cirrhosis. In general, HCC develops in ≥ 1% of patients with cirrhosis per year. Can we predict who will develop HCC and can we prevent this evolution ? We have to learn from the natural history of the disease. Let us consider some data : 1) all forms of cirrhosis can lead to HCC, irrespective of the aetiology. 2) the aetiology determines the age, at which HCC develops, and the incidence e.g. metabolic disorders such as tyrosinaemia, will lead to HCC already in children. HCC due to HBV-cirrhosis occurs usually 10 yrs earlier than in alcoholics, and HCC due to HCV-cirrhosis originates mostly even later. 3) combinations of factors speed up the evolution e.g. aflatoxin with HBV, and alcohol with HCV. 4) treatment of the aetiology of the cirrhosis can prevent or retard the evolution. This is seen in successfully treated haemochromatosis and HBV-cirrhosis (e.g.prevention of neonatal infections by vaccination in Taiwan, and prevention of HCC by interferon-induced HBeAg seroconversion (3). Interferon treatment of HCV might also prevent later development of HCC but really convincing data are not yet available.

Do we have parameters to predict development of HCC in an individual case ? Studies in Japan both with ultrasonography and levels of AFP document a variable progression. Often an upsurge after a variable period of stable disease is present (4). Better biological and morphological markers are therefore needed to predict imminent changes of a regenerative nodule into a neoplastic one. Recently, soluble IL2R has been proposed as a new tumour marker (5). The pattern of contrast captation in MRI also needs further study to characterise early HCC.

Treatment possibilities of non-resectable, non-transpantable HCC (late cases)

1. *Chemotherapy* : at present, a clearcut effect of any single drug or combination of drugs has not been proven. A recent study proposed further investigation of the combination of epirubin with etoposide (6).
2. *Tamoxifen* : although initial data showed some effect and more so in female than in male patients, larger studies could not substantiate a beneficial effect (7-9).
3. *Intratumoural injection of ethanol, acetic acid etc. via the percutaneous route (PEI).* The aim is to produce coagulation necrosis together with microvascular thrombosis in order to arrest tumour growth and spreading. Under ultrasonography, 99% ethanol mixed with some xylocaine is injected after careful local anaeshesia of the skin and liver capsule. The injection is repeated daily for a number of times equal to twice the diameter in cm. Most groups restrict the application to tumours < 3 or < 4 cm (10-12) although some have treated larger tumours (13). The average 3 and 5 yr survival of patients with Child's A or B cirrhosis reported is 50-70% and 30-50% respectively (10-12).These figures compare favourably with those obtained by resection, however randomised studies to directly compare with surgery (12) or with expectant attitude have rarely been made. In most studies, development of new lesions at another site occurs during followup, more often than local recurrence.

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This would point to the importance of a therapy aimed at secondary prevention (see sub 6). The natural evolution of small lesions is very variable ; some studies documented a 2 yrs survival without therapy as being identical to that of patients undergoing resection (14,15). Comparative studies are thus needed. A possible drawback of PEI is the risk of tumour seeding in the needle track. This is estimated to occur in ≥ 1% of cases (16).

4. *Radiofrequency ablation (RFA).* Just as with intratumoural ethanol injection, this procedure aims at necrosis of the HCC. The technique is being investigated at various centers and preliminary data comparing RFA with percutaneous ethanol injection seem to show some advantage in favour of RFA (17). RFA produces thermic necrosis due to a high frequency alternating current (200-1200 kH2). Tumours till 5 cm can easily become necrotic. Further evaluation is necessary to delineate indications and contra-indications.
5. *Embolisation, chemolipiodolisation, chemolipioembolisation (TACE).* Japanese studies showed an effect of arterial embolisation on the survival of HCC (18). This was further developed into chemolipioembolisation combining the property that lipiodol enters tumour tissue through the aberrant capillary wall of HCC and remains in tumour tissue for a prolonged time, with emulsification of doxorubicin or cis-platinol in the lipiodol. If the portal vein is open, "microembolisation" can be added. Studies have demonstrated that extensive necrosis of HCC is obtained (19). In general, quality of life of the patients improves but clear-cut gain in survival is not obvious. We matched treated with untreated patients according to Okuda's and Child's criteria and observed a 9 month gain in survival in the treated group (20). Obviously, the number is too small to reach strong conclusions. Two large multicenter studies (21,22) did not see a significant effect on survival ; however, if the NEJM-paper (22) is analysed in detail, a benefit for the treatment group is present at all time points except at the end. This may be due to the presence in the non- treated group of some patients with a very slowly progressing tumour. Personally, I feel that chemolipiodolisation is effective in a subgroup of patients but we still have to define their characteristics (23). Better results are obtained if lipiodol stays in the tumour for a prolonged period of time (24,25). The optimal dose and the frequency of injection remain to be defined. The combination of radiolabelled lipiodol with chemolipiodol also deserves study since the mechanism of action differs (26). The combination of percutaneous ethanol injection with TACE seems better than either therapy alone (27).
6. *Retinoids.* Cyclic retinoids such as polyprenoic acid, bind with great affinity to retinoid receptors and exert a growth-inhibition effect. They seem to induce clonal deletion of premalignant and latent malignant cells (28). When given to patients having undergone a previous resection or PEI of a HCC, treatment with polyprenoic acid was shown to retard or prevent new development of secondary HCC (29) and to prolong 6 yr survival from 46% in the placebo to 74% in the treated group (30). Oral ß-all-transretinoic acid, given as first treatment to patients with a HCC did not seem efficient (31).
7. *Somatostatin analogs : octreotide or lanreotide* (32,33). Preliminary studies in small numbers of patients with HCC point to a tumour-suppressive effect of these ST-analogs resulting in increased survival and reduced AFP levels. Trials with larger numbers of patients are needed to confirm or dispute an effect of ST-analogs.
8. *Gene therapy.* Several investigators have reported successful necrosis of chemically-induced or implanted liver tumours in animals by recombinant-adenovirus-mediated transfer of genes. Transfection with the *wild type p53 gene* (because a mutant p53 protein has been found in 30-50% of human HCC, ref34) via the hepatic artery led to a 50% reduction of the number of tumour nodules and of liver weight (35). Kanai *et al.* (36) transfected the gene encoding for *Cytosine Deaminase* (CD) with AFP as promo/or/enhancer. CD stimulates the transformation of the antifungal drug 5 Fluoro-Cytosine into the cytotoxic agent 5 Fluoro-Uracil. Rats bearing a tumour cell line underwent transfection and received the non-toxic 5 FC. It is locally transformed in the tumour tissue and the resulting high amounts of 5 FU resulted in necrosis with a 70-85% reduction of tumour tissue. Others (37,38) transfected the thymidine-kinase gene of the Herpes Simplex Virus. Two days later, Ganciclovir is administered I.P. with ensuing necrosis of the liver tumours in 2/3 of the rats. Although these data are still preliminary, they open exiting perspectives to obtain tumour necrosis in vivo.

Conclusions

HCC is at the increase in the Western World. Screening by ultrasonography every 6 months has been advocated for early detection. The prime therapy remains surgical resection or orthotopic liver transplantation. Data from Japan suggest that oral acyclic retinoids partly prevent or retard later development of secondary tumours. When not feasable, percutaneous ethanol injection alone or combined with transarterial chemolipiodolisation or chemolipioembolisation seems to offer advantages in some, yet ill-defined groups of patients. Somatostatin-analogs should be studied further. In all studies, it is very important to reach a sufficient number of patients and to compare with a group with a well-documented natural history (39,40).

A variety of procedures using gene therapy look promising ; these investigations in animals need further refinement.

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