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TOPIC HIGHLIGHT

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Hepatocellular carcinoma in developing countries: Prevention, diagnosis and treatment

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Abstract

Hepatocellular carcinoma (HCC) occurs commonly and with increasing frequency in developing countries, where it also carries an especially grave prognosis. The major risk factor for HCC in these regions is chronic hepatitis B virus (HBV) infection, although dietary exposure to aflatoxin B1 also plays an important etiological role. Prevention of HCC in developing regions is unlikely in the foreseeable future. Although an effective vaccine against HBV is available, the percentage of babies born in developing countries that receive the full course of immunization remains low. Moreover, the usually long interval between infection with HBV and the development of HCC means that 30 to 50 years will elapse before the full effect of the vaccine will be realized. Practical measures to prevent aflatoxin B1 exposure are not in place. Serum α-fetoprotein levels are a useful pointer to the diagnosis of HCC in low-income countries, but definitive diagnosis is hampered both by the lack of the sophisticated imaging equipment now available in developed countries and by obstacles to obtaining histological proof. In the majority of patients in low-income regions, the tumor is inoperable by the time the patient presents. Hepatic resection is seldom possible in sub-Saharan Africa, although the tumor is successfully resected in a larger number of patients in China. Liver transplantation for HCC is rarely performed in either region. Sophisticated new radiotherapy techniques are not available in developing countries. The beneficial effects of the multikinase inhibitor, sorafenib, are encouraging, although financial considerations may restrict its use in low-income countries.

Key words: Hepatitis B virus infection; Aflatoxin B_1; α-fetoprotein; Hepatic resection; Hepatic transplantation; Sorafenib

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common human cancer, with approximately 750 000 new cases occurring worldwide each year[1]. Eighty percent of global HCCs occur in developing countries, and in these countries HCC is one of the three most common tumors. Eastern and south-eastern Asia (with the exception of Hong Kong, Japan, South Korea, Singapore, Taiwan and Macau) and almost all of sub-Saharan Africa are low-income regions with high incidences of the tumor[1].

HCC ranks third in annual global cancer mortality rates and has the shortest survival time of any cancer in

both males and females[2]. The prognosis is even poorer in patients in low-income countries. Among the reasons for the poor prognosis are the often advanced stage of the tumor when the patients are first seen and that optimal management of HCC requires resources that are seldom available in developing countries.

The reason for the high incidence of HCC in resource-poor countries is that two of the three major environmental causes of the tumor worldwide, namely, chronic hepatitis B virus (HBV) infection and dietary exposure to the fungal toxin, aflatoxin B_1, occur far more often in these countries. Chronic HBV infection occurs in more than 8% (and in as many as 15%) of the population and, of those infected, one-quarter or more will develop the tumor[2]. The virus is responsible for 80% to 89% of HCCs in these regions, where HBV infection is almost always acquired in infancy or early childhood, as a result of either perinatal or horizontal transmission of the virus. Ninety percent of those infected in the first year of life, decreasing to 50% those infected in the fifth year and far fewer of those infected in the next few years, will become chronically infected with the virus and face a life-time relative risk of developing the tumor as high as 100%[3]. With chronic HBV infection being acquired predominantly in infancy or early childhood, the resultant HCC presents before or in mid-adulthood, the most productive years of life, causing a drain on productive capacity in addition to a substantial burden on the healthcare system. The reasons for the poorer prognosis of HCC in low-income countries are the generally longer interval before the patients receive medical attention and hence the more advanced stage of the tumor at the time of diagnosis, the fewer doctors and the scarcity and inferior quality of the diagnostic facilities available, and the limited treatment that can be offered. In addition, financial and logistical constraints in resource-poor regions compromise attempts to prevent the tumor.

Aflatoxins are difuranocoumarin derivatives of Aspergillus flavus and A.parasiticus. These fungi contaminate crops, particularly maize, ground nuts and fermented soy beans, in tropical and sub-tropical countries with warm, humid climates and, more especially, in subsistence farming communities in these countries. Contamination occurs both during growth of the crops and as a result of their improper storage. Sub-Saharan Africa and the Asia-Pacific region have high levels of exposure to the fungal toxin. Aflatoxin B_1 (AFB_1) is the aflatoxin most often found in contaminated human foodstuffs and is the most potent hepatocarcinogen[4]. The hepatocarcinogenic effects of AFB_1 and HBV are synergistic, with a multiplicative relative risk for HCC development[5].

With few exceptions, chronic hepatitis C virus (HCV) and HCV-induced HCC are significantly less common in developing than in developed countries. One exception is Somalia, where chronic HCV infection is as common as chronic HBV infection[6].

In most rural regions of China, the population drinks primarily pond, ditch or river water. High concentrations of tumor-promoting microcystins, derived from blue-green algae, have been identified in these waters and high microcystin contents correlate with a high incidence of HCC[7,8].

PREVENTION

Because of the high incidence, inadequate treatment and graver prognosis of HCC in low-income countries, prevention of the tumor is an urgent priority in these countries.

Prevention of hepatitis B virus-induced hepatocellular carcinoma

An effective and safe vaccine against HBV has been available for a number of years. Based on data in 2008, HBV vaccine was included in the expanded Program of Immunization in 177 countries and an estimated 69% of the birth cohort that year received 3 doses of the vaccine[9]. Unfortunately, the percentage of babies born in resource-poor countries that receive the full course of immunization is far lower that that in developed countries. In sub-Saharan African countries, between 10% (in Chad) and 99% (in The Gambia) of babies receive the full course of the vaccine[10]. In 12 countries, less than 70% of infants receive the full course[10]. The coverage is even worse in the Asia-Pacific region.

In Taiwan (not a low-income country), where immunization of babies against HBV began in 1984 and universal coverage was achieved by 1986, coverage of all preschool children by 1987 and extension to older children and adults by 1990, the vaccination program has already resulted, in the age groups that have been immunized, in a decrease from 90 to 15% in the number of infected babies born to highly infectious carrier mothers and a ten-fold or more decrease in the rate of chronic HBV carriage in these babies, as well as in those infected slightly later by horizontal infection[11]. The prevalence of HCC among recipients of the vaccine has already decreased by 70% in comparison with those in the non-vaccinated age groups[12]. After adjustment for age and sex, the relative risk for HCC was 0.31 among children aged 6 to 19 years in the vaccinated cohort, compared with similar aged children in unvaccinated cohorts[11]. These encouraging results give promise that the universal incorporation of a full program of HBV vaccination into the Expanded Program of Immunization in developing countries in which HBV infection is endemic will, in the future, prevent thousands of deaths from cirrhosis and HCC and that HBV-induced HCC could ultimately be completely prevented.

In the early years after immunization was introduced, some cases of chronic HBV infection and HCC were still seen in Taiwanese children and adolescents who had received a full course of the vaccine. This led to the realization of the importance of administering hyperimmune γ-globulin (HBIG) at the time of birth (in spite of its high cost) in addition to the first dose of the vaccine

to babies born to highly infectious (HBeAg-positive) carrier mothers. Addition of HBIG to the vaccine schedule has resulted in a further reduction in the occurrence of chronic HBV infection and HBV-induced HCC[11]. Regrettably, the high cost of HBIG will have important implications in low-income countries. In the few individuals still developing "break-through" infections and tumors in Taiwan, failure to complete the full course of the vaccination program has been shown to be responsible[11].

Because of the usually long interval between infection with HBV and the development of HCC, it will take 30 to 50 years for the full effect of the vaccine on the incidence of HBV-induced HCC to be realized in these countries. In the interim, the incidence of HBV-induced HCC continues to increase.

Prevention of aflatoxin B_1-induced hepatocellular carcinoma

Contamination of staple foodstuffs by AFB_1 does not occur in high-income countries because those food stuffs that might be infected are screened for their aflatoxin content by governmental agencies and do not enter the commercial market if unacceptably high levels are found. In low-income countries, regulations to control dietary exposure to AFB_1 are either non-existent or unenforceable in practice. Contaminated crops are consumed by the subsistence farmer's family, neighbors, friends and relatives, and are sold locally or regionally without ever coming under the scrutiny of a governmental agency. It is estimated that about 45 million of the world's population are exposed to aflatoxins.

Because contamination by Aspergillus species takes place both during growth of the crops and as a result of their improper storage, attempts at primary prevention must be directed at minimizing both sources of fungal contamination[4,13-15]. One possible intervention is to alter the agricultural practices in regions of high dietary AFB_1 intake by replacing crops that are highly susceptible to fungal contamination with others at lower risk. This approach has been successfully used in one limited study in China when a change to a rice-based diet resulted in an appreciable decrease in AFB_1 intake[13,14]. However, for most communities in resource-poor countries, a change in agricultural practices leading to a change in diet is not feasible. Because damaged plants are more susceptible to fungal contamination, relatively simple and inexpensive pre-harvest prevention could be achieved by adequate irrigation and spraying of the crops with fungicides[13-15]. A study confirming the effectiveness of combating post-harvest contamination by simple interventions such as sun-drying the crops on cloth rather than the earth, hand sorting to remove mouldy crops, and better storage practices has been reported[15]. For such interventions to be successful on a wide scale in resource-poor countries will require training of the farmers in practical ways to prevent contamination of susceptible crops and the provision of appropriate storage facilities[15].

Prevention of hepatitis C virus-induced hepatocellular carcinoma

Despite considerable research over many years into the development of a vaccine against HCV, there appears to be little likelihood that a vaccine will become available in the near future. In both developed and developing countries, attempts at prevention of HCV infection (which also apply to HBV infection) should include encouraging the avoidance of the high risk behaviors of illicit drug injection and promiscuous sexual activity, insisting on the use of needles and syringes on a single occasion only, or if this is not possible, careful sterilization before their reuse, and on sterilization of surgical instruments[16]. Equally important is encouraging the screening of donated blood for the presence of these viruses[16].

Despite recent advances in treating patients with chronic HCV infection with anti-viral drugs, the overall impact of therapy is small because the majority of individuals chronically infected with the virus are unaware that they are infected. The high cost of the anti-viral agents is an additional impediment in developing countries. Efforts to prevent infection should include identifying persons at increased risk of HCV infection and providing them with appropriate counseling.

Prevention of microcistin-induced hepatocellular carcinoma

Since 1973, the Chinese government has been urging the rural population to drink deep-well water[17]. This has resulted, for example in Qidong county, in 80% of the population now drinking deep-well water compared with only 20% in earlier years. However, the effect of this intervention on the occurrence of HCC has yet to be published.

DIAGNOSIS

Because of the higher incidence of HCC in developing countries, medical practitioners in these countries are more likely than those in low incidence regions to be mindful of this tumor. Moreover, history taking and physical examination can be performed equally well in resource-poor as in resource-rich regions and, in all but the most impoverished or remote regions, the least expensive of organ imaging techniques, ultrasonography, may be available. It should therefore be possible in low-income countries to make a provisional diagnosis of HCC or, at least, to include the tumor in the differential diagnosis. Moreover, the diagnostic laboratories should be able to measure the serum α-fetoprotein (AFP) concentration. The serum AFP concentration is particularly useful in the diagnosis of HCC in low-income regions[18,19]. The level is raised in 90% of sub-Saharan black Africans with HCC and in 75% of the patients it is raised to a level higher than that which may be present in benign hepatic diseases (usually given as greater than 400 or 500 ng/mL)[18,19]. In Chinese patients, approximately 75% have a raised serum

AFP level, with about 50% having a level above 400 ng/mL[20,21]. In contrast, the value is raised in only approximately 55% of patients in developed countries[22].

Definitive diagnosis of HCC depends upon either histological examination of the hepatic mass or the finding with a dynamic imaging technique of one or more mass-lesions in the liver showing a typical vascular profile in the form of early arterial phase enhancement, followed by washout with loss of the enhancement. Micro-bubble contrast ultrasonography, three-dimensional contrast-enhanced computerized spiral tomography or magnetic resonance imaging enhanced with gadolinium or gadoxetic acid will not be available in the rural areas and may not even be available in the cities of resource-poor countries.

In developing countries, fewer medical (or para-medical) practitioners than their counterparts in high-income countries are trained to perform percutaneous liver biopsies. Moreover, it is necessary to send the biopsy material to a central diagnostic laboratory to have the histological examination performed. In practice therefore, particularly in rural regions of developing countries, the tumor is often diagnosed on the basis of the clinical features and either a raised serum AFP concentration or, less often, the finding of a mass-lesion on ultrasonography of the liver, without obtaining histological confirmation. Furthermore, because of the poor results of treating HCC and dismal prognosis of the patients in developing countries, many medical practitioners, particularly those in the rural areas, develop a nihilistic attitude to definitive diagnosis and treatment of the tumor and the patient is often sent home to die on the basis of a provisional diagnosis only.

HCC is frequently diagnosed only when the tumor has reached an advanced stage. This applies in all geographical regions but more so in developing countries. A further difficulty in resource-poor countries is the insufficient number of hospital beds available.

In all geographical regions, HCC commonly co-exists with cirrhosis[23]. However, the effect of the associated disease on the diagnosis of the tumor differs between developed and developing regions. In the former, HCC often presents as a complication of long-standing symptomatic cirrhosis and the patient may have few, if any, symptoms attributable to the tumor, whereas in the latter, the presence of cirrhosis is typically overshadowed by the symptoms and signs of the tumor[23].

Although HCC generally presents clinically in a sufficiently characteristic way to allow the presence of the tumor to be suspected by an experienced clinician, it may manifest in any of a number of unusual ways, at least some of which occur more commonly in patients in developing countries. Unusual presentations of HCC may result from a number of complications of the tumor, such as tumor rupture causing an acute hemoperiteum, Budd-Chiari syndrome and inferior venal caval obstruction from invasion of the hepatic venous system and inferior vena cava by the tumor, and obstructive jaundice from spread of the tumor into the biliary tree. Atypical presentations may also result from paraneoplastic manifestations of the tumor, the more common of which are hypoglycemia, polycythemia, and hypercalcemia[24]. A physical sign that is a useful pointer to the diagnosis of HCC but is often missed is the presence of a hepatic arterial bruit. The systolic bruit, which is heard in as many as 27% of patients with HCC[25], is focal and its detection requires thorough auscultation over the liver.

The finding of an elevated right hemidiaphragm (or rarely left hemidiaphragm) on chest X-ray is a useful pointer to the presence of HCC in developing countries[26], provided that an amebic liver abscess, another common space-occupying hepatic lesion in these countries and one that can present clinically in a manner not dissimilar to HCC, can be excluded. Multiple pulmonary metastases are often evident in patients with HCC in resource-poor regions at the time of first admission[26,27] and this finding in association with a pathologically raised right hemidiaphragm on chest X-ray is virtually diagnostic of HCC.

Serum markers of HCC, reactivity of AFP with Lens culinaris agglutinin (AFP-L3), des-γ-carboxy prothrombin and α -fucosidase, have not proved to be more useful than AFP as indicators of HCC in resource-poor countries.

The use of a 6-month surveillance program consisting of a physical examination, measurement of the serum AFP level and ultrasonographic examination of the liver aimed at the early detection of HCC is beyond the means of resource-poor countries, even if the ultrasonographic facilities are available.

TREATMENT

The first decision that needs to be taken when a definitive diagnosis of HCC has been made is whether or not the tumor is resectable.

Hepatic resection

Unfortunately, in resource - poor regions, HCC is very often inoperable at the time the diagnosis is made. Apart from the advanced stage of the tumor resulting from the difficulty and delay in obtaining medical advice, in many patients in these regions, HCC runs a particularly fulminant course and has reached an advanced stage by the time the patient seeks medical attention. Little information has been published on the rate of growth of the tumor in these patients, but in one study, based on serial estimations of serum AFP levels in black African patients, the doubling time of HCC was estimated to be as short as 10 d[28]. This time contrasts with an average tumor doubling time as long as 136 d in patients in resource-rich countries[29,30].

Even in those patients in developing countries in which the tumor runs a less rapid course and who come under medical attention timeously, early detection may be difficult. Because of the large size of the liver, the tumor must grow to an appreciable size before it can be felt or before it invades adjacent structures. Moreover, the considerable functional reserves of the liver ensure that jaundice and other evidence of hepatic dysfunction appear only when a

large part of the organ has been replaced by tumor.

Only 8% of Ugandan[31] and 1% of rural southern African black patients[32] were found to have resectable tumors, at a time that resectability rates of up to 37% were being recorded in some western countries with low or intermediate incidences of HCC[33] and up to 20% in Japanese patients[34]. These resection rates have not changed significantly in sub-Saharan Africa in more recent times, whereas resectability rates in industrialized countries are now appreciably higher. However, hepatic resections have been performed more often in some of the larger hospitals in China.

Further evidence for the advanced stage of HCC when patients from developing countries first present is the often large size of a single tumor or the extent of the tumor burden when more than one tumor mass is present in the liver. This too has important implications when considering the operability of the tumor. The average weight of the cancerous liver at necropsy in African black patients with HCC ranges in different studies from 3045 to 3914 grams (with a largest size of 8780 grams) (the average weight of a normal liver in an adult black male is 1750 grams)[35-37]. This contrasts with average weights of 2036 grams in Japanese[38], 2615 grams in North American[36] and 2477 grams in South African Caucasian patients[35-37]. The tumors are generally even larger in non-cirrhotic livers (average weights of the tumorous liver in Ugandan patients without cirrhosis is 4134 grams compared with 2768 grams in those with cirrhosis[38]) and the same is true in southern African blacks (3918 and 3085 grams, respectively)[35]. Multiple tumor masses throughout the liver, irrespective of their size, obviously preclude hepatic resection. Moreover, resection of one or a few small tumor masses may be precluded by its or their position in the liver.

Another reason for the low resectabilty rates of HCC when patients from resource-poor countries are first seen is the frequency with which the tumor has already spread beyond the liver. For example, 19% of southern African blacks with HCC have radiologically-evident pulmonary metastases at this time[26,27] (compared, for instance, with 7% in patients in the United Kingdom[22]). Moreover, in a further 27% of these patients, pulmonary metastases too small to have been seen radiologically during life were present at necropsy, performed on average only 6 wk later[26].

Cirrhosis is present in about 70% of patients with HCC in developing countries (although in some regions of sub-Saharan Africa it is present less often than in patients in other parts of the world) and this too greatly influences the decision whether or not surgical resection will be possible. The resulting liver dysfunction may make surviving the operation impossible or unlikely. In addition, the presence of cirrhosis precludes post-operative regeneration of the remaining liver tissue. In all populations, the requirements for hepatic resection in a patient in whom HCC has arisen in a cirrhotic liver are that the serum bilirubin level should be normal, significant portal hypertension and esophageal varices should be absent, and the platelet count should be above 100 000/mm[39].

Careful follow-up of patients from all regions after successful surgical resection of HCC is mandatory because of the high recurrence rate of the tumor, which may be as high as 50% at 3 years and 70% at 5 years[39]. Apart from incomplete resection of the original tumor, the reasons for HCC recurrence are that new tumor foci develop subsequently because the cause of the malignant transformation is still present in the remaining liver tissue. In addition, the possibility exists that malignant cells in the circulation, increased in number by the handling of the tumorous liver during the operation[40,41], may seed the liver post-operatively. Tumors caused by chronic HBV infection are often multifocal and small tumors missed at the time of the original surgery may become clinically evident at any time thereafter. Those patients in whom the tumor has been resected but who are still actively infected with HBV or HCV must be treated with appropriate anti-viral drugs with the aim of curing the infection or, if this is not possible in the case of HBV, of seroconverting HBV e antigen-positive patients to an anti-HB e-positive status and keeping the viral loads at as low a level as can be achieved.

Hepatic transplantation

With the generally far advanced stage of HCC at the time that patients in resource-poor countries seek medical attention, very few meet the criteria required for liver transplantation (no spread of the tumor beyond the liver, a single tumor less than 5 cm in diameter or fewer than three tumor masses, each less than 3 cm in diameter and no macrovascular invasion (Milan criteria)[26]). Few, if any, hepatic transplants have been performed for the treatment of HCC in developing countries.

Other treatments

In patients with inoperable HCC, improved results are now being obtained with the use of 3-dimensional high-dose photon beam radiotherapy and stereotactic radiotherapy. However, the sophisticated equipment necessary for these therapies are not available in resource-poor countries. Similarly, forms of local treatment or palliation of HCC, such as radio-frequency ablation, ablation with alcohol or trans-arterial chemoembolization, which are available in high-income countries, require equipment and expertise that are unlikely to be available in low-income countries.

For those patients in whom surgery or palliation cannot be performed, drug therapy needs to be considered. Up until recently, no form of chemotherapy has been found to be effective in the treatment of HCC[42]. The reasons for the poor results are the late presentation with very large tumor burdens and perhaps the frequency of multi-drug resistance genes. However, recent studies have shown the beneficial effects on survival time of the oral multikinase inhibitor, sorafenib. Trials with this and other multikinase inhibitors have and are being conducted in a number of centers in different parts of the world but, as

far as I am aware, no results have yet been published in patients in resource-poor countries. In addition, the cost of the drug may be an important issue in low-income countries.

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