



CHALLENGES OF MANAGING HEPATOCELLULAR CARCINOMA IN SUB-SAHARA AFRICA

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ABSTRACT

The high incidence of hepatocellular carcinoma (HCC) in sub-Saharan Black Africans and the advanced stage of the disease when the patients usually seek medical attention, as well as the inadequate diagnostic and, more importantly, treatment facilities for the tumour pose enormous challenges in managing HCC in sub-Saharan Africa. At present HCC in Black Africans is seldom amenable to surgical intervention, in the form of either resection or transplantation, at the time the diagnosis is made. An immediate challenge will be to provide the expertise and facilities that will make it possible to increase the number of patients amenable to and undergoing successful surgical treatment, and to have available to the many patients chronically infected with hepatitis B virus (or less often hepatitis C virus) anti-viral agents that will prevent postoperative tumour recurrence. A further immediate challenge is the provision of expertise in locoregional therapy with transarterial chemoembolization, percutaneous ethanol injection, or radiofrequency ablation for downstaging inoperable tumours to meet the requirements for either resection or transplantation. The introduction of molecular targeted therapies that act on pathways critical for cancer progression and survival has created a new hope for the effective chemotherapy of inoperable HCC. Positive results have been reported in populations other than Black Africans with the use of Sorafenib, an oral multikinase inhibitor, and trials urgently need to be conducted in Black African patients. Other major challenges, in the longer term, in managing HCC in sub-Saharan Africa are presymptomatic detection of the tumour and prevention of hepatitis virus infections, dietary exposure to aflatoxin, and dietary iron overload, the major causes of HCC in Black Africans.

INTRODUCTION

Although data on the incidence of hepatocellular carcinoma (HCC) in sub-Saharan Africa are incomplete and significantly underestimate the true incidence of the tumour, HCC is undoubtedly one of the most common malignant tumours in the sub-continent and is the major cause of death from cancer, accounting for approximately 200,000 deaths each year¹. HCC in Black Africans carries a particularly grave prognosis, average survival times from the onset of symptoms being as short as 14 weeks^{2,3} and, with very few exceptions, all of the patients surviving for less than one year (annual fatality ratio 0.97). The great majority of the population live in rural areas where the incidence of the tumour is higher than it is in urban

areas and where facilities for diagnosing and treating HCC are least adequate. HCC often occurs at a relatively young age in Black Africans, and this is even more evident in those born and growing up in rural areas. Men are affected far more often than are women.

The occurrence of HCC at such high incidence in Black Africans and the advanced stage of the disease when the patients usually seek medical attention, as well as the inadequate diagnostic and, more importantly, treatment facilities for the tumour, pose an enormous challenge in managing HCC in sub-Saharan Africa.

DIAGNOSIS

A histological diagnosis of HCC is seldom made in rural areas of sub-Saharan Africa, and even in large

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urban hospitals the tumour is often diagnosed on the basis of the clinical features and either a raised serum α -fetoprotein concentration or the finding of a mass-lesion on imaging the liver, without obtaining histological confirmation. Because of the dismal prognosis and poor results of treating HCC in sub-Saharan Black Africans, many medical practitioners in the sub-continent have a nihilistic attitude to definitive diagnosis of the tumour, and the patient is often sent home to die on the basis of a provisional diagnosis only. A further difficulty is the insufficient number of hospital beds available in relation to the large number of patients in all disciplines requiring admission to most hospitals in the subcontinent. Compounding the problem is the paucity of clinicians trained to perform liver biopsies and the insufficiency of imaging equipment and diagnostic histopathology facilities. Early diagnosis of the tumour is, therefore, a great challenge in attempting to effectively manage HCC in sub-Saharan Africa.

Although HCC often presents clinically in a sufficiently characteristic way to allow the presence of the tumour to be suspected by an experienced clinician, it may manifest in any of a number of unusual ways. Clinicians, whether working in rural or urban hospitals or clinics, must familiarize themselves with these presentations. 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 bruit, which is present in as many as 27% of patients with HCC⁴, is focal and its detection requires thorough auscultation over the liver. Unusual presentations of HCC result either from a number of complications of the tumour, such as tumour rupture causing an acute haemoperitoneum, Budd-Chiari syndrome and inferior venal caval obstruction from invasion of the hepatic venous system and inferior vena cava, and obstructive jaundice from spread into the biliary tree, or from paraneoplastic manifestations of the tumour, the more common of which are hypoglycaemia, polycythaemia, and hypercalcaemia⁵.

The finding of an elevated right hemidiaphragm (or rarely left hemidiaphragm) on chest xray is a useful pointer to the presence of HCC in Black Africans⁶, provided that another common space-occupying hepatic lesion in sub-Saharan Africa that presents clinically in a manner not dissimilar to HCC, namely, amoebic hepatic abscess, can be excluded. Multiple pulmonary metastases are often evident in Black Africans with HCC at the time of first admission⁶, and this finding in association with a pathologically raised

right hemidiaphragm is virtually diagnostic of HCC. Most hospitals in the larger African cities now have at least one means of imaging the liver to confirm the presence of a mass-lesion, but this is not true of rural clinics or hospitals. The serum α -fetoprotein concentration has proved to be a more useful serum marker of HCC in Black Africans than it is in populations living in industrialized countries^{7,8}. Approximately 90% of Black African patients have a raised value, but more importantly in about 75% of patients the level can be regarded as diagnostic (variously quoted as more than 400ng/ml or 500ng/ml). The reactivity of α -fetoprotein with *Lens culinaris* agglutinin improves the diagnostic usefulness of α -fetoprotein as a tumour marker⁹, but it is a more complicated and expensive laboratory investigation and is better suited to industrialized countries. Other diagnostic assays such as des-gamma-carboxy prothrombin and α -L-fucosidase have not proved to be more useful than α -fetoprotein as indicators of HCC in Black Africans^{10,11}, although this is probably true in industrialized countries. A number of recently described putative serum markers of the tumour, such as glypican-3, have yet to be evaluated in Black Africans.

Histological demonstration of the features of HCC is required for definitive diagnosis.

TREATMENT

Treatment of HCC in Black patients in sub-Saharan Africa has been and remains largely unrewarding. Improving this highly unsatisfactory state of affairs is an urgent and major challenge for medical services in the sub-continent.

Surgical resection

Once a definitive diagnosis of HCC has been made anywhere in the world, the first decision that needs to be taken is whether or not the tumour is resectable and, if not, would a liver transplant be curative. In sub-Saharan Africa this decision is best made in urban medical centres with experience in managing HCC and having the required facilities to do so. Regrettably, in many Black Africans HCC runs a particularly fulminant course and has reached an advanced stage by the time the patient seeks medical attention. Little information is available on tumour doubling times in Black Africans with HCC, but in one study, based on serial estimations of serum α -fetoprotein levels, the tumour doubling time was estimated to be as short as 10 days¹². This time contrasts with an average doubling time of 60 to 136 days in other populations studied¹³⁻¹⁵. Even in those



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patients with a less rapid course, early detection is difficult. Because of the large size of the liver, the tumour 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 tumour.

For these reasons HCC is rarely resectable in Black Africans at the time the diagnosis is made. For example, only 8% of Ugandan¹⁶ and 1% of rural southern African Blacks¹⁷ were found to have resectable tumours at a time that resectability rates of up to 37% were being recorded in some industrialized countries with a low or an intermediate incidence of HCC¹⁸ and up to 20% in Japanese patients¹⁹. These rates have not changed significantly in sub-Saharan Africa in more recent times, whereas resectability rates in industrialized countries are now appreciably higher.

One of the reasons for the irresectability of HCC when the Black African patient is first seen is the frequency with which the tumour has already spread beyond the liver. For example, 19% of southern African Blacks with HCC have radiologically-evident pulmonary metastases at this time^{6,20} (compared, for instance, with 7% in patients in the United Kingdom²¹). Moreover, in a further 27% of the patients pulmonary metastases too small to have been seen radiologically during life are present at necropsy, performed on average only 6 weeks later⁶. Admittedly, some of the latter metastases might have been prevented by timely surgical intervention.

Further evidence for the advanced stage of HCC when the patients first present is the often large size of a single tumour or the extent of the tumour burden when more than one tumour mass is present in the liver. This too has important implications when considering the operability of the tumour. 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)²²⁻²⁴. This contrasts with average weights of 2036 grams in Japanese²⁵, 2615 grams in North American¹⁹, and 2477 grams in South African Caucasian patients²²⁻²⁴. The tumours 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 cirrhosis¹⁶, and the same is true in southern African Blacks (3918 and 3085 grams, respectively)²². Multiple tumour masses throughout the liver,

irrespective of their size, obviously preclude hepatic resection. Moreover, resection of one or a few small tumour masses may be precluded by its or their position in the liver.

Cirrhosis is present in a significant proportion of Black African patients with HCC (although in some regions of the sub-continent 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 attendant detrimental effects on liver function may make surviving the operation unlikely. In addition, the presence of cirrhosis precludes post-operative regeneration of the remaining liver tissue. Thus, 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 oesophageal varices should be absent, and the platelet count should be above 100,000/mm³²⁶. The often advanced stage of HCC when the patient is first seen and the effects of the associated cirrhosis are the reasons why a small minority only of Black Africans have a resectable tumour.

Careful follow-up of all patients after successful surgical resection of HCC is mandatory because of the high recurrence rate of the tumour, which may be as high as 50% at 3 years and 70% at 5 years²⁷. Apart from incomplete resection of the original tumour or an inadequate resection margin, the reasons for HCC recurrence are that new tumour 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 operation²⁸, may seed the liver post-operatively.

The dominant cause of HCC in sub-Saharan Blacks is chronic hepatitis B virus (HBV) infection. Tumours caused by this virus are often multifocal, and new tumours may become clinically evident at any time. Those patients in whom the tumour has been resected but who are still actively infected with HBV must be treated with appropriate anti-viral drugs with the aim of curing the infection or, if this is not possible, 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. Thus far, only post-operative administration of interferon- α has achieved any success in preventing tumour recurrence²⁹. It is essential that more effective antiviral agents, which are expensive and not readily available in Africa at present,



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must be made available to the patients that require them.

The challenge in sub-Saharan Africa is to provide the expertise and facilities that will make it possible to increase the number of Black patients undergoing successful surgical resection of HCC to the level now achieved in industrialized countries, and to have available to those patients chronically infected with HBV (or less often hepatitis C virus (HCV)) anti-viral agents that will prevent postoperative tumour recurrence. Careful and prolonged follow-up of the patients is essential.

Liver transplantation

In most countries patients with HCC who, for one or more reasons, are not candidates for hepatic resection are considered for liver transplantation. This operation offers the possibility both of curing the tumour and of replacing the cirrhotic liver with a healthy liver. In industrialized countries present day survival rates for liver transplantation for HCC exceed 70% at 5 years, survivals comparable with those in patients receiving a liver transplant for diseases other than HCC²⁶. However, with the generally far advanced stage of the tumour at the time that Black African patients seek medical attention, very few meet the criteria required for liver transplantation (no spread of the tumour beyond the liver, and a single tumour less than 5 cm in diameter or fewer than three tumour masses, each less than 3 cm in diameter (Milan criteria²⁶). Furthermore, facilities for liver transplantation are extremely limited in sub-Saharan Africa and very few, if any, such operations are currently being performed. Accordingly, no information on the results of liver transplantation for HCC in sub-Saharan Black Africans is available.

The challenge will be to develop centres of expertise in liver transplantation in selected African urban hospitals. These centres could also be responsible for the liver resections for HCC. This initiative will require the creation of suitably equipped facilities, training of surgeons to do the operations, anaesthetists to anaesthetize the patients, often with severely compromised liver function, nurses to provide the necessary post-operative observation and care, and physicians to administer the necessary drugs to prevent rejection of the transplanted liver and, in the case of HBV- (or less often HCV)-induced tumours, anti-viral drugs to prevent tumour recurrence in the transplanted liver. Tumour recurrence after liver transplantation is a far lesser problem than it is after hepatic resection of HCC but early seeding of the transplanted liver by

malignant cells in the circulation is one possible explanation. Sophisticated laboratory facilities to monitor the progress of the patients postoperatively will also have to be made available.

Locoregional downstaging therapy

An important strategy to improve the frequency and results of liver resection or transplantation in patients with HCC is downstaging of an inoperable tumour either to meet the requirements for surgical resection or the Milan criteria for liver transplantation. This is achieved by using locoregional therapy with one or more therapeutic modalities, including transarterial chemoembolization, percutaneous ethanol injection (PEI), or radiofrequency ablation (RFA)³⁰. In industrialized countries downstaging can be achieved in up to 70% of the patients in whom this is attempted³⁰. In addition, these techniques may be curative in their own right in a small percentage of patients. They have yet to be used on a large scale in sub-Saharan Africa and no reports of the results obtained have been published. The expertise needed to perform these down-sizing techniques and the necessary equipment should be established in the centralized treatment facilities designed to perform the surgical interventions.

Radiotherapy

No stratified randomized trials have yet shown that conventional radiotherapy is of value in the treatment of HCC in Black Africans, or indeed in any population. However, recent innovations in radiation therapy, such as three dimensional high-dose photon radiotherapy, may play a role in treating patients with inoperable tumours³¹. The information available on this and other novel irradiation approaches in the treatment of Black African patients is very limited, and if these modalities of treatment are to be introduced the necessary equipment and expertise in using the equipment will have to be made available.

Chemotherapeutic agents

A large number of anticancer agents, given alone or in combination, and by intravenous or intra-arterial routes, have been administered to Black Africans with HCC without achieving a significant response rate³². This is also true of biological response modifiers³². These results were worse than those in other populations, although in no population has chemotherapy been considered in the past to be very effective. The reasons for the poor results in Black African patients are the late presentation of these

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patients, often with very large tumour burdens, and perhaps a higher incidence of multi-drug resistance genes.

Recent developments in the chemotherapy of HCC have, however, been more encouraging. A more comprehensive knowledge of the molecular pathogenesis of HCC has revealed the importance of activation of growth signaling pathways, including multiple receptor tyrosine kinase pathways, and inactivation of key tumor-suppressor genes in the pathogenesis of the tumour^{33,34}. The introduction of molecular targeted therapies that act at pathways that are critical for cancer progression and survival has created a new hope for the effective chemotherapy of HCC. Positive results have been reported with the use of Sorafenib, an oral multikinase inhibitor, which inhibits tumor-cell proliferation and tumor angiogenesis and increases the rate of apoptosis in a wide range of tumor models^{33,34}. A randomized phase III double-blind placebo-controlled trial in a large series of patients with advanced HCC, treated with Sorafenib showed a 3-month survival improvement³⁵. The median overall survival was 10.7 months with Sorafenib compared with 7.9 months with placebo. Median time to progression was 5.5 months with Sorafenib versus 2.8 months with placebo.

Trials with this and other multikinase inhibitors are now being conducted in a number of centres in different parts of the world, but as far as I am aware no results have yet been published in Black African patients. The challenge will be to undertake trials in the sub-continent to determine the efficacy of these drugs in Black African patients.

Early diagnosis

If the results of surgical intervention or medical management of HCC in Black Africans are to be improved in the future, early diagnosis of the tumour is essential and this too poses an enormous challenge. Earlier diagnosis will entail educating the public at large, including, and in particular, rural dwellers, about HCC, the symptoms with which it presents, and the need to seek medical attention as soon as symptoms appear. It will also need medical practitioners, particularly those in rural hospitals or clinics, to be made aware of the importance of early diagnosis and speedy referral to a medical centre suitably equipped for the comprehensive management of the patient. Even early diagnosis may not help those patients in whom HCC runs a particularly fulminant course.

Yet another challenge in the management of HCC in sub-Saharan Africa will be to detect the tumour before it becomes symptomatic.

Presymptomatic detection

Programmes for detecting presymptomatic HCC are of two kinds. The first is screening of whole populations known to have a very high incidence of the tumour, and the second long-term surveillance of individuals known to be at increased risk of developing the tumour. Because of the high incidence of HCC in sub-Saharan Africa, the former approach was attempted in the 1970s, but with very little success^{12,36} and has not been attempted since. In the latter approach, the individuals monitored are, in the main, those with chronic HBV or HCV infection or cirrhosis of any cause. Ideally, Black Africans now known to have one or more of these conditions should be seen at six monthly intervals and the serum α -fetoprotein level measured and an ultrasound examination of the liver performed in an attempt to detect early, surgically amenable tumours. Comprehensive surveillance and diagnosis algorithms for the early diagnosis for HCC are available³⁷.

A further challenge in the African context will be to establish facilities for undertaking this form of surveillance, particularly in the context of chronic HBV infection, in as many rural and urban centres as is possible.

The ultimate challenge in managing HCC in the Black African will, of course, be to prevent rather than attempt to cure this devastating tumour. This goal will require the elimination of the major causes of HCC as it occurs in the sub-continent, in particular chronic HBV infection, but also dietary exposure to the fungal toxin, aflatoxin B₁, chronic HCV infection, and dietary iron overload in the African.

PREVENTION

Prevention of chronic HBV infection could be achieved by the universal inclusion of the HBV vaccine in the Expanded Programme of Immunization in all sub-Saharan countries. At present, most but not all of these countries have immunization programmes in place, often sponsored by the Global Alliance for Vaccine Immunization (GAVI) in association with the World Health Organization (WHO) and other non-governmental organizations, and the WHO estimates