Hepatocellular Carcinoma: Hope and Challenges

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Cancer of the liver and intrahepatic bile ducts is the sixth commonest cancer in the world, with approximately 841,000 new cases reported in 2018. The commonest primary liver tumor is hepatocellular carcinoma [HCC] [approximately 75 percent], followed by cholangiocarcinoma, comprising most of the remaining cases [1]. In addition, primary liver cancer is the third most frequent cause of cancer-related mortality in the world, with over 780,000 deaths in 2018 [2]. With a five-year survival of 18 percent, liver cancer is the second most lethal tumor after pancreatic cancer [3]. In Pakistan prevalence of HCC varies from 3.7%-16% of malignant tumours with viral hepatitis associated cirrhosis being the commonest etiology [4-5]. There is geographic variation in the incidence of HCC with 72 percent of cases occurring in Asia.

Cirrhosis from any cause is a risk factor for developing HCC. It was estimated that up to one-third of patients with cirrhosis will develop HCC during their lifetime, with an annual incidence rate of 1 to 8 percent, based on long-term follow-up studies. In Pakistan, approximately 87%of HCC is caused by viral hepatitis either C (68%) or B related cirrhosis (22%) [4-5]. Other risk factors include alcohol; environmental toxins like aflatoxin B1; metabolic factors like nonalcoholic fatty liver disease, diabetes mellitus, obesity; genetic diseases like hemochromatosis, alpha -1 antitrypsin deficiency, and acute intermittent porphyrias.

Primary liver cancer incidence and mortality rates have been increasing in many parts of the world, including North America, Latin America, and central Europe. However in the United States; a decline is noted in these rates from 2016 to 2018. It has been attributed to the increased detection of localized HCC [6-8]. HCC has a median subclinical period of 3.2 years. In this period screening has the highest impact with early detection and potential for cure [9, 10]. Ultrasound (US) can detect tumors as small as 1.6±0.6 cm [11]. Although US has sensitivity and specificity of >90% in detecting HCC, its efficiency is compromised in liver cirrhosis and is operator-dependent. Asian Oncology Summit (AOS) recommends 3–6 monthly US with serum AFP. AOS guidelines are the least stringent given the high incidence of risk factors (hep-B and hep-C) and HCC in this region. In addition, AOS recommends an AFP > 400 ng/mL to be diagnostic for HCC in high-risk patients. As low as 10% of patients in Pakistan with risk factors for HCC undergo regular screening and the majority of patients are diagnosed when they are symptomatic. For those who are screened; US and AFP are the most frequently performed investigations but the time duration between these investigations, cut-off for elevated AFP, and sonographers' technical competency remain grey areas [12, 13]. Because of the late diagnosis and aggressive nature median survival following diagnosis is approximately 6 to 20 months. Although the mainstay of therapy is surgical resection, the majority of patients are not eligible because of tumor extent or underlying liver dysfunction. The lack of skilled hepatobiliary surgeons and transplant centres increases our challenges. In unresectable localised disease with tumors ≤3cm in size and ≤ 3 in number ablation therapies [RFA, MWA] or stereotactic body radiotherapy [SBRT] can be performed. For tumors 3 to 5 cm in size combination of ablation and transarterial chemoembolisation [TACE] is suggested. Radiation therapy [RT] can be an alternative. For tumors larger than 5cm in unresectable localised disease TACE, radioembolisation, SBRT are the treatment options depending upon tumor characteristics, location and local expertise. In cases of portal vein invasion radioembolisation, SBRT, combination of TACE and RT [if preserved unilateral flow] are suggested. In presence of extrahepatic disease or progression of disease systemic therapy should be undertaken provided the patient has a good liver reserve and performance status. With poor performance status and Child class C, the best supportive care should be offered.

Until 2008, no effectual therapy existed for patients with advanced-stage HCC or those failing local therapies. However, there has been a revival of hope and zeal for systemic therapy of HCC with the emergence of data showing that the molecularly targeted agents sorafenib and regorafenib improve survival compared with best supportive care alone. Afterward, a survival benefit has also been shown in the second-line setting for nivolumab, an immune checkpoint inhibitor, single-agent lenvatinib has shown noninferiority to first-line sorafenib, and most lately, the combination of atezolizumab plus bevacizumab was better to front-line sorafenib in the IMBrave 150 trial. These results have drastically altered the treatment and prognosis for advanced HCC.

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Multiple specialties: surgery, radiation oncology, medical oncology, and interventional radiology contribute to an array of therapies for HCC. Multidisciplinary assessment and planning, mostly supervised by hepatologists, usually evolve into more intensively evaluated recommendations and are less likely to evolve into a recommendation for a treatment for which a single health care professional has expertise but that may not be the best treatment for an individual patient. Keeping in mind the increasing burden of HCC and limited resources available in health care in Pakistan, it is of paramount importance to promote multidisciplinary and research culture. It is indeed a wake-up call for society in general and health care professionals in particular.

The majority of patients with HCC have underlying liver disease. Patients who undergo any form of therapy for HCC are at high risk for progression to liver failure because of their underlying liver disease, and proper monitoring, assessment, and treatment of the underlying liver disease may have a major impact on long-term survival.

In Pakistan, most of the patients present late in the advanced stage of disease making chemotherapy even more important to cater to this vast group of patients. The same applies to TACE. Screening for hepatitis B and C should be done vigorously with clinical and imaging surveillance to detect HCC in localised early stage.

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