tumor regrowth. Second, the Sorafenib HCC Assessment Randomized Protocol (SHARP) phase III trial of sorafenib versus placebo for unresectable HCC showed that survival could be significantly enhanced in the treatment arm with only 2% of the patients having tumor response but 70% of patients having disease stabilization. This observation has led to a reconsideration of the usefulness of response and the significance of disease stability. Third, HCC is a typically highly vascular tumor, and the vascularity is considered to be a measure of tumor viability. As a result, the Response Evaluation Criteria in Solid Tumors (RECIST) have been modified to mRECIST, which requires measurement of vascular/viable tumor on the CT or MRI scan. A partial response is defined as a 30% decrease in the sum of diameters of viable (arterially enhancing) target tumors. The need for semiquantitation of tumor vascularity on scans has led to the introduction of diffusion-weighted MRI imaging. Tissue-specific imaging agents such as gadoxetic acid (Primovist or Eovist) and the move to functional and genetic imaging mark a shift in approaches. Furthermore, plasma AFP response may be a biologic marker of radiologic response.

TREATMENT SUMMARY

Long-term survival is associated with resection or ablation or transplantation, all of which can yield >70% 5-year survival. Liver transplant is the only therapy that can treat the tumor and the underlying liver disease simultaneously and may be the most important advance in HCC therapy in 50 years. Unfortunately, it benefits only patients with limited size tumors without macrovascular portal vein invasion. Untreated patients with multinodular asymptomatic tumors without vascular invasion or extrahepatic spread have a median survival of approximately 16 months. Chemoembolization (TACE) improves their median survival to 19–20 months and is considered standard therapy for these patients, who represent the majority of HCC patients, although ^{90}Yttrium therapy may provide similar results with less toxicity. Patients with advanced-stage disease, vascular invasion, or metastases have a median survival of around 6 months. Among this group, outcomes may vary according to their underlying liver disease. It is this group at which kinase inhibitors are directed.

SUMMARY (TABLE 111-5)

The Most Common Modes of Patient Presentation

1. A patient with known history of hepatitis, jaundice, or cirrhosis, with an abnormality on ultrasound or CT scan, or rising AFP or DCP (PIVKA-2)
2. A patient with an abnormal liver function test as part of a routine examination
3. Radiologic workup for liver transplant for cirrhosis
4. Symptoms of HCC including cachexia, abdominal pain, or fever

History and Physical Examination

1. Clinical jaundice, asthenia, itching (scratches), tremors, or disorientation
2. Hepatomegaly, splenomegaly, ascites, peripheral edema, skin signs of liver failure

Clinical Evaluation

1. Blood tests: full blood count (splenomegaly), liver function tests, ammonia levels, electrolytes, AFP and DCP (PIVKA-2), Ca^{2+} and Mg^{2+}; hepatitis B, C, and D serology (and quantitative HBV DNA or HCV RNA, if either is positive); neurotensin (specific for fibrolamellar HCC)
2. Triphasic dynamic helical (spiral) CT scan of liver (if inadequate, then follow with an MRI); chest CT scan; upper and lower gastrointestinal endoscopy (for varices, bleeding, ulcers); and brain scan (only if symptoms suggest)
3. Core biopsy: of the tumor and separate biopsy of the underlying liver

Therapy (Tables 111-5 and 111-6)

1. HCC <2 cm: RFA, PEI, or resection
2. HCC >2 cm, no vascular invasion: liver resection, RFA, or OLTX
3. Multiple unilobar tumors or tumor with vascular invasion: TACE or sorafenib
4. Bilobar tumors, no vascular invasion: TACE with OLTX for patients with tumor response
5. Extrahepatic HCC or elevated bilirubin: sorafenib or bevacizumab plus erlotinib (combination agent trials are in progress)

OTHER PRIMARY LIVER TUMORS

FIBROLAMELLAR HCC (FL-HCC)

This rarer variant of HCC has a quite different biology than adult-type HCC. None of the known HCC causative factors seem important here. It is typically a disease of younger adults, often teenagers and predominantly females. It is AFP-negative, but patients typically have elevated blood neurotensin levels, normal liver function tests, and no cirrhosis. Radiology is similar for HCC, except that characteristic adult-type portal vein invasion is less common. Although it is often multifocal in the liver, and therefore not resectable, metastases are common, especially to lungs and locoregional lymph nodes, but survival is often much better than with adult-type HCC. Resectable tumors are associated with 5-year survival ≥50%. Patients often present with a huge liver or unexplained weight loss, fever, or elevated liver function tests on routine evaluations. These huge masses suggest quite slow growth for many tumors. Surgical resection is the best management option, even for metastases, as these tumors respond much less well to chemotherapy than adult-type HCC. Although several series of OLTX for FL-HCC have been reported, the patients seem to die from tumor recurrences, with a 2- to 5-year lag compared with OLTX for adult-type HCC. Anecdotal responses to gemcitabine plus cisplatin-TACE are reported.

Epithelioid Hemangioendothelioma (EHE) This rare vascular tumor of adults is also usually multifocal and can also be associated with prolonged survival, even in the presence of metastases, which are commonly in the lung. There is usually no underlying cirrhosis. Histologically, these tumors are usually of borderline malignancy and express factor VIII, confirming their endothelial origin. OLTX may produce prolonged survival.

Cholangiocarcinoma (CCC) CCC typically refers to mucin-producing adenocarcinomas (different from HCC) that arise from the biliary tract and have features of cholangiocyte differentiation. They are grouped by their anatomic site of origin, as intrahepatic (IHC), perihilar (central, ~65% of CCCs), and peripheral (or distal, ~30% of CCCs). IHC is the second most common primary liver tumor. Depending on the site of origin, they have different features and require different treatments. They arise on the basis of cirrhosis less frequently than HCC, but may complicate primary biliary cirrhosis. However, cirrhosis and both primary biliary cirrhosis and HCV predispose to IHC. Nodular tumors arising at the bifurcation of the common bile duct are called *Klatskin* tumors and are often associated with a collapsed gallbladder, a finding that mandates visualization of the entire biliary tree. The approach to management of central and peripheral CCC is quite different. Incidence is increasing. Although most CCCs have no obvious cause (etiology unknown), a number of predisposing factors have been identified. Predisposing diseases include primary sclerosing cholangitis (10–20% of primary sclerosing cholangitis [PSC] patients), an autoimmune disease, and liver fluke in Asians, especially *Opisthorchis viverrini* and *Clonorchis sinensis.* CCC seems also to be associated with any cause of chronic biliary inflammation and injury, with alcoholic liver disease, choledocholithiasis, choledochal cysts (10%), and Caroli's disease (a rare inherited form of bile duct ectasia). CCC most typically presents as painless jaundice, often with pruritus or weight loss. Diagnosis is made by biopsy, percutaneously for peripheral liver lesions, or more commonly via endoscopic retrograde cholangiopancreatography (ERCP) under direct vision for central lesions. The tumors often stain positively for cytokeratins 7, 8, and 19 and negatively for cytokeratin 20. However, histology alone cannot usually distinguish CCC from metastases from colon or pancreas primary tumors. Serologic tumor markers appear to be nonspecific, but CEA, CA 19-9, and CA-125 are often elevated in CCC patients and are useful for following response to