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LIVER CANCER: APPROACHING A PERSONALIZED CARE

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Abstract:

In the last decades, the understanding and knowledge regarding the intrahepatic cholangiocarcinoma (iCCA) and hepatocellular carcinoma (HCC) has been improved. Scientific research has made it possible to diagnose the liver cancer at the molecular level and provide optimal treatment to the patients to a maximum extent. The initial step, which is considered a landmark for future liver cancer management, was the discovery of TP53 hotspot mutation.

In a nutshell, while decades ago the field of liver cancer was perplexing with grim perspectives, limited clinical data and research trials, it has now evolved into a competitive field with multiple advancements, research work and trials based evidence at a constant rate. Positive outcomes in preventive approaches, eliminating risk factors, understanding molecular mechanism, and better treatment chemistry will further increase the status of this field, and it might will exclude liver cancer from top 5 cancer killers.

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INTRODUCTION:

In the last decades, the understanding and knowledge regarding the intrahepatic cholangiocarcinoma (iCCA) and hepatocellular carcinoma (HCC) has been improved. Scientific research has made it possible to diagnose the liver cancer at the molecular level and provide optimal treatment to the patients to a maximum extent. The initial step, which is considered a landmark for future liver cancer management, was the discovery of TP53 hotspot mutation. [1,2] Moreover, development of ultrasound, computed tomography and MR have been instrumental in on-time disease diagnosis. At present, if properly applied, then several treatment options with positive outcomes are available. Major highlights encompass: i) acceptance of liver transplantation for HCC if it meets the Milan criteria, ii) recognizing ablation as a possible curative option, iii) TACE benefit proof, and iv) incorporation of sorafenib (an effective systemic therapy). These all methods are clinically approved and keep on advancing from time to time. [3,4] This review paper encapsulates the data surrounding current recommendations for clinical practice, specifically locoregional approach regarding TACE and TARE.

EPIDEMIOLOGY:

Around the globe, liver cancer is the second major cause of death, including both HCC and iCCA. Its incident rate is still on hype, but as the risk factors are well known now, so its prevention is an achievable aim. Reduction in alcohol consumption and control of hepatitis B and C infections would leave a huge positive impact upon the liver health. On the screen, other important risk factors have appeared like metabolic syndrome and overweight.

If the exposure to risk factors are reduced, then the mortality rate can be controlled. Because early diagnosis can lead to effective treatment and long term survival rate. This objective is applied in a population at risk for HCC. Patients who enter screening, upon diagnosis, should be able to undergo treatment for HCC. If comorbidities or end stage liver disease is not leading the patient towards transplant exist, then screening and diagnosis along with treatment will be of no benefit. Moreover, accurate diagnostic options should be available. Unfortunately, a large number of patients remain undiagnosed with cirrhosis.

Molecular Pathogenesis and Signalling Pathways:

For better understanding of biological subcalsses and cancer drivers, and to evaluate the positive outcomes of molecular therapies, molecular classification has played a significant role. From the Biological perspective, various classes have been characterized including Proliferation class, Wnt subclass (CTNNB1 mutations and HCV etiology), and an inflammation class. The proliferation subclass have 50% cases with tumors derived from progenitor cells and tends to have a worse prognosis. Nonetheless, no subclass has been reported so far as very response to a specific targeted therapy. [4]

Data has reported several mRNA based molecular signatures in tumoral and non-tumoral adjacent tissues. Signatures like CK19, and EPCAM 3 display worse prognosis. Moreover, a 5 gene score signature including TAF9, RAN, RAMP3, KRT19, and HN1 genes displayed better overall survival rate in four cohorts of Asian and Caucasian patients. In parallel, in HCC prognosis there is immense importance of tumor microenvironment in liver tissues. It is found that molecular profiling together with major clinical predictors and assessment of risk of HCC and death along with analysis of factors like portal hypertention degree, concomitant treatments during follow up, coffee consumption or sustained alcohol intake and other comorbidities will permit more personalized approach. [5,6]

Screening, Diagnosis and Staging:

Screening based upon ultrasound examination must be carried out every 6 months for HCC in populations at risk. For advanced disease and poor prognosis, alpha-fetoprotein (AFP) acts as a predictor. Hence, even if some kind of tumors are detectable via AFP, they would not likely to belong to early cancer stage.

The aim of screening is to diagnose solitary tumors ≤20 mm, when the curative treatment has high chances and vascular invasion or intrahepatic spread is low. Accurate biopsy or imaging is extremely difficult in the diagnosis of cirrhotic liver with <10mm nodules, as they are not malignant. Thus, proper diagnostic approach is opted when nodule size exceeds 10mm. If in arterial phase this nodule presents increased contrast uptake, followed by contrast washout in delayed phases of CT or MR then it is easy to diagnose without biopsy confirmation. [7,8] however, if the pattern isn't specific then biopsy is mandatory to diagnose iCCA. AFP again here has limited use, and PET has no diagnostic value.

Evaluation of the patients to predict prognosis should be based upon liver function, tumor burden and general status of health. Cancer related symptoms is linked with poor outcome. Child pugh should not be considered a single evaluating block as it does not allow proper stratification. But, parameters like renal failure, encephalopathy, bacterial peritonitis,

hyponatremia and other end stage liver diseases depicts a need of transplant evaluation. [7,8]

MELD has also limited capacity for discrimination if the liver function is not at the end stage. Indeed, if in the absence of HCC liver function would favor liver transplant, then the presence of HCC will create a contradiction for it. These kind of patients must be classified as end stage.

Locoregional Approach:

In the treatment of intermediate HCC stage, locoregional approach is widely used. This approach encompasses conventional TACE (cTACE), ablation, TACE with drugeluting beads (DEB-TACE), transarterial radioembolization (TARE) and hepatic arterial infusion chemotherapy and external radipotherapy.

Microwave ablation is a promising option for ablating larger tumors, but long term follow up data is still required, same is the case with high intensity focused ultrasound. RFA is the first line technique but with HCC >3cm increase, its failure rate also increases.

Intravenous administration of ThermoDox delivers higher concentrations of anti-cancer drugs directly to the FPA ablation zone's periphery, where post treatment tumor recurrence is very common. Unfortunately, a phase III trial showed negative outcomes comparing ThermoDox plus RFA with RFA alone. RFA and TACE combination has also been evaluated, it did show improved efficacy, but the robust evidence is missing beyond the RFA optimal profile.[9]

The sphere usage has shown positive outcomes as it slowly releases chemotherapy while obstructing the arterial blood supply (DEB-TACE) and improves tolerance and standardization. DEB-TACE has anthracycline loaded beans unlike conventional lipiodol-anthracycline emulsions. The positive outcome of this method is the sustained release of drug within the tumor with less drug exposure and higher drug concentration. Owing to this, negative outcomes of systemic chemotherapy are significantly reduced. [10, 11] The prominent issue in TACE is to abide by the guidelines that when to start or stop the therapy. This therapy is suitable for patients without cancer related symptoms and compensated liver disease, extrahepatic spread or vascular invasion. TACE therapy can be restarted upon disease progression. However, if the specific criteria are absent or TACE fails to induce response at the progression time as in liver failure, vascular invasion, or symptomatic disease, then it should not be repeated. The median survival time of the patients treated with TACE should exceed 3 years, as per data.

Arterial embolization induces hypoxic tumor microenvironment by releasing pro-angiogenic factors like VEGF and PDGF, which adversely affect the prognosis of patients. This situation leads to the rationale combination of TACE with sorafenib, as the latter inhibits the action of pro-angiogenic factors. This combination is considered to be the safest one, but adjustments are still needed. [12, 13]

Significant activity has been observed from the TARE. A complex activity is needed for its setting, and this specificity limits its widespread use. It acts by delivering resin or glass loaded spheres with a radiation agent that are pure β-emitters like Yttrium-90 or Holmim-166. [14, 15] TARE has less adverse outcome sin comparison to the TACE. However, actinic damage is predicted to appear after treatment for months and this require a pragmatic evaluation about the amount of radiation required to treat the tumor and measure the risk associated with multifocal, large HCC both lobes. Severeal studies have depicted survival rate similar to TACE therapy and sorafenib, especially in patients with portal vein thrombosis and advanced stage HCC. [16, 17] Ongoing trials should define the comparative outcomes and the values of TARE and TACE.

HAIC, on the other hand, consists of a selective infusion of chemotherapy, which is inserted through a chemo port into the tumor feeding hepatic artery. It provides a high dose of anti-cancer drug to the localized spot, where the first pass effect in the liver is expected. This effect reduces systemic concentration and prevent drug related adverse effects. Despite its widespread usage, the survival rate is still unknown about this drug.

High dose focal external radiation therapy, including stereotactic body radiation therapy, can be used to treat progressed HCC without or with portal vein thrombosis. It is observed that if the tumor targeted therapy is used, then Actinic damage can be avoided of the non tumoral liver and the surrounding structures. Alone or a combination with other treatments can be used. Selective radiation of HCC early stage might be a niche in comparison with the percutaneous options. [18]

Overview of iCCA Management:

The 7th edition of the recent guidelines endorse the AJCC/UICCA staging system and surgical support

resection as the choice of treatment for iCCA, specifically for patients with single intrahepatic nodules and no dissemination. Contrastly, patients with vascular invasion, lymph node metastases or intrahepatic metastases, should not undergo resection. No specific options for first-line local-regional therapeutic options for patients with non-resectable iCCA are recommended under randomized controlled trials. Cisplatin and gemcitabine is a systemic practice standard of therapy for iCCA in patients with ECOG performance status from 0 to 1, but the data are too specific to make an established standard criteria for care. [19]

Liver transplantation is highly controversial for iCCA patients. The reports depict that liver transplantation is difficult to summarize the presented non-standardization selection criteria, disparate neoadjuvant treatment protocols and a small number of patients. In most of the transplant centers, iCCA is considered a contradiction based upon its high recurrence rates. However, this practice has recently been challenged, as in cirrhotic patients with iCCA ≤2 cm in diameter may undergo liver transplantation without recurrence. But, further research and data is mandatory to support these findings and to clarify either prognosis of a mixed tumor is worse or not than for HCC. [20]

In a nutshell, while decades ago the field of liver cancer was perplexing with grim perspectives, limited clinical data and research trials, it has now evolved into a competitive field with multiple advancements, research work and trials based evidence at a constant rate. Positive outcomes in preventive approaches, eliminating risk factors, understanding molecular mechanism, and better treatment chemistry will further increase the status of this field, and it might will exclude liver cancer from top 5 cancer killers.

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