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CURATIVE THERAPY FOR HEPATOCELLULAR CARCINOMA: A REVIEW

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ABSTRACT

Hepatocellular carcinoma (HCC) is a type of liver cancer that is becoming more frequent. A variety of potentially curative treatments have become accessible as a result of advancements in surgical techniques and technology, as well as the development of molecular-target medications. The treatment of HCC patients is determined on the stage of their cancer. Although liver resection remains the treatment of choice for very early-stage HCC, local ablative therapy is posing a threat. HCC is the most common type of primary liver cancer and the second-leading cause of death worldwide. HCC is more common in persons with liver cirrhosis in the Western world. As a result, the use of locoregional therapies and systemic agents should be based on a multidisciplinary assessment, which should include, above all, consideration of the functional liver reserve. The current treatment lines and novel tactics in the management of HCC are summarised in this study.

Keywords: Hepatocellular carcinoma, Curative intent treatment, Targeted Agents.

INTRODUCTION

Primary liver tumours are the fifth most prevalent malignancy and the third leading cause of cancer-related death worldwide, with an estimated annual mortality rate of 548,000. Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer, accounting for 70–85 percent of all cases. Hepatitis B virus infection (HBV), hepatitis C virus infection (HCV), chronic liver illness (of any cause), and hereditary metabolic abnormalities are all known risk factors for the development of HCC. HCC rates are more than twice as high in men around the world, which may be partly due to greater incidence of viral hepatitis among male patients.[1]

Both the incidence of HCC and the prevalence of underlying etiologic risk factors for HCC vary significantly by region. HCC is more common in East and Southeast Asia, as well as Africa. The lowest

incidences of HCC are found in Western Asia and Europe. The major risk factors associated with the development of HCC in Europe, North America, and Japan include HCV (50–70 percent of cases), HBV (10–20 percent of cases), alcohol-related cirrhosis (20 percent of cases), and other/idiopathic causes (20 percent of cases) (10 percent cases). In North America, nonalcoholicsteatohepatitis is becoming more widely recognised as a risk factor for HCC.HBV is responsible for 70% of HCC cases in Asia and Africa; HCV, alcoholic cirrhosis, and other/idiopathic causes account for the remaining 10%. HCC is more common in people with HCV who have extensive fibrosis or cirrhosis, but it can also happen in patients with chronic HBV who do not have fibrosis or cirrhosis.[2]

Over the last 25 years, the incidence of primary liver cancer in the United States has risen from 2.6 to 8.1 instances per 100,000. This development is likely caused in part by rising prevalence of HCV-related hepatitis and the obesity epidemic. HCC has become one of the top causes of cancer mortality in the United States throughout the same time period. HCC is a major worldwide health problem, and improving outcomes for HCC patients has the potential to benefit a large number of people all over the world. [3]

Primary screening for HCC

Active screening increases survival in patients with chronic liver disease by detecting HCC at an early stage. A randomised controlled trial compared individuals aged 35–59 years with HBV or chronic hepatitis who had an AFP level and a liver ultrasound every 6 months to those who did not. Despite mediocre (58.2 percent) protocol adherence, screening was linked to a 37 percent reduction in HCC-related mortality. Furthermore, screening was linked to a much higher detection of resectable HCC, with 46.5 percent of patients in the screened group undergoing resection compared to just 7.5 percent in the control group.The authors urged for the introduction of screening programmes for high-risk populations based on these findings, claiming that more screening compliance would result in a bigger reduction in mortality.

The American Association for the Study of Liver Disease (AASLD) updated their screening recommendations for persons at risk of HCC in 2010. Patients with chronic liver illness, such as those with HCV, HBV, or autoimmune hepatitis, should be screened. Ultrasound was indicated as the primary screening method every 6 months; AFP was not recommended in this situation because to a lack of sensitivity and specificity. The National Comprehensive Cancer Network currently advises screening with both AFP and ultrasonography every 6–12 months for people who have hepatitis B without cirrhosis and for all patients with cirrhosis. [4]

Curative intent treatment modalities for HCC

When an HCC is diagnosed, the patient's underlying liver function and comorbidities, as well as tumor-related variables, influence the therapeutic approach. The size and location of the tumour, its relationship to neighbouring tissues, the number of lesions, the existence of vascular invasion, and the presence of extrahepatic illness are all tumor-related characteristics that influence therapy options for HCC. The presence of ascites, portal hypertension, thrombocytopenia, cirrhosis, or fibrosis in the native liver, as well as the estimated volume of the future hepatic residual following resection, all influence the therapy of HCC.When creating a treatment plan, it's also important to consider the patient's functional state and comorbidities.[5]

Resection, transplantation, ablation, intra-arterial therapy, and systemic therapy are the five treatment options now available for HCC. Embolization and systemic therapy, on the other hand, are normally reserved for individuals who are not candidates for curative intent therapy. The choice of the best therapeutic modality for a given patient can be difficult, and it should be done in a multidisciplinary setting involving experts in hepatobiliary and transplant surgery, hepatology, interventional radiology, medical oncology, and radiation oncology, as recommended by current National Comprehensive Cancer Network guidelines. [6]

It's debatable whether excision or transplantation is the chosen curative intent treatment for people with early stage HCC. In noncirrhotic individuals or those with mild cirrhosis and enough functional liver reserve, resection for HCC is an option. Resection is particularly well suited for individuals who have substantial underlying liver reserve but are not transplant candidates. Resection can be done in patients with big tumours and multifocal disease, unlike transplantation, which has strict tumor-specific selection requirements. 5-year overall survival (OS) rates for all patients after HCC resection have been reported to range from 42–62 percent, with disease free survival (DFS) rates ranging from 30 to 40 percent[7].

However, other writers have found that partial hepatectomy in patients with early HCC who are otherwise transplantable has a greater long-term survival rate, which may even be comparable to that of liver transplantation. For example, after hepatic resection, Izumi reported a 5-year survival rate of more than 75% in patients with a solitary HCC tumour without vascular involvement. Unfortunately, the majority of HCC patients have advanced HCC or poor underlying hepatic function, making resection as a therapy option impossible. [8]

Risk factors for recurrence and patterns of recurrence

HCC recurrence following curative purpose surgery is fairly common, as previously stated. Recurrence following resection can occur in 60–70% of individuals, although recurrence after ablative therapy has been reported to be as high as 80%. Despite the fact that transplantation is linked to a decreased rate of

intrahepatic recurrence, total recurrence might occur in up to 20% of individuals. Recurrence after curative intent therapy for HCC has been shown to be influenced by a number of factors relating to both the initial tumour and the underlying liver. Hepatitis status (especially chronic HCV infection), vascular invasion, tumour size of 3 cm, and the presence of numerous lesions are all independent predictors of recurrence. [9]

Patients with HCV had a higher rate of poorly differentiated HCC, vascular invasion, and cirrhosis than HBV patients, as well as a higher rate of intrahepatic recurrence. Patients with HCV-related HCC have an incrementally increased DFS with transplant compared to resection when compared to those with HBV or no hepatitis, according to recent studies.[10]

Molecular Targeted Agents

Sorafenib

Sorafenib is an oral kinase inhibitor that inhibits tumour proliferation by inhibiting serine/threonine kinases of C-Raf, wild-type B-Raf, and mutant B-RafV600E, which are components of the Raf / MEK / ERK pathway (MAPkinase pathway) downstream of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and epithelial growth factor receptor (EGFR), as well as by suppressing angiogenesis through inhibition of tyrosine kinases such as VEGFR1, VEGFR2, VEGFR3, PDGFRβ, RET, and FLT-3 (fms-related tyrosine kinase-3) [11]

In two big trials (the SHARP trial and the Asia-Pacific study), sorafenib was proven to significantly prolong overall survival (OS) over placebo, and it has since become the standard therapy for advanced HCC.

Current Landscape of Molecular Targeted Drug Development for HCC

To date, a number of clinical studies for new molecularly targeted medications have been conducted. The trials can be divided into four broad categories:

(1) Adjuvant therapy after curative therapy

(2) Combination therapy with TACE

(3) First-line therapy for advanced HCC

(4) Second-line therapy for advanced HCC

Results of phase III trials are described below.

Prevention of Recurrence after Curative Therapy (Adjuvant Therapy)

To date, three phase III trials have been conducted: one comparing vitamin K2 to placebo as adjuvant chemotherapy after radiofrequency ablation or resection, one comparing sorafenib to placebo (STORM trial), one comparing peretinoin to placebo (NIK333 trial), and one comparing ablation plus lyso-thermosensitive liposomal doxorubicin. However, in Japan, South Korea, and Taiwan, a peretinoin trial

in patients with HCC associated with hepatitis B is presently underway. After curative therapy, a phase III trial comparing the anti-programmed death (PD)-1 antibody nivolumab to placebo is also ongoing[12]

Combination Therapy with TACE

Three trials of sorafenib combination therapy with TACE, namely, a phase III trial in Japanese and Korean patients (Post-TACE trial), a phase II trial comparing sorafenib plus TACE with drug-eluting beads (DEB-TACE) to placebo plus DEB-TACE (SPACE trial), and a phase III trial also investigating sorafenib combination with DEB-TACE (TACE 2 trial), have been conducted to date,but all of them failed due to not meeting the primary end points of prolonging time to progression (TTP) or progression-free survival (PFS). Phase III trials of the molecular targeted agents, brivanib and orantinib, in combination with TACE, were also conducted, but they also failed due to not meeting the primary endpoint of prolonging OS [13]

The definition of "progression" for TACE trials as an outcome was redesigned based on the lessons learned from these five failed trials, better reflecting how TACE is performed in clinical practise. The first positive trial to demonstrate the clinical efficacy of TACE plus sorafenib (TACTICS trial) was presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium in 2018, using this newly defined "progression." PFS was significantly longer with TACE plus sorafenib in the TACTICS trial than with TACE alone (25.2 months vs. 13.5 months).

First-Line Therapy for Advanced HCC

Overview of First-Line Trials Conducted to Date

Sorafenib was compared to single-agent sunitinib, brivanib, and linifanib in head-to-head trials, but none of them were able to show superiority or non-inferiority to sorafenib. All phase III trials comparing sorafenib plus erlotinib, doxorubicin, or hepatic arterial infusion chemotherapy (HAIC) with an implanted reservoir system to sorafenib alone failed. Two randomised controlled studies comparing radio embolization with Y90 to sorafenib were likewise unsuccessful[14]

Lenvatinib:

Overview of REFLECT Trial Results

During this 10-year era of failed studies, the REFLECT study was the only one with a positive outcome.Lenvatinib is an oral kinase inhibitor that selectively inhibits receptor tyrosine kinases involved in tumor angiogenesis and tumor growth (e.g.,VEGFR1,VEGFR2,VEGFR3, fibroblast growth factor receptor (FGFR)1, FGFR2, FGFR3, FGFR4, PDGFRα, KIT, and RET). In advanced HCC, a single-arm phase II trial produced good outcomes (TTP: 7.4 months; OS: 18.7 months) [15]

The REFLECT trial, which compared sorafenib and lenvatinib in a phase III trial, was then conducted. The REFLECT study was a global phase III experiment that looked at whether lenvatinib was better than

sorafenib. Patients were divided into four groups according on their race (Asian or non-Asian), vascular invasion and/or EHS (yes or no), Eastern Cooperative Oncology Group performance status (PS) (0 or 1), and body weight (60 kg or 60 kg). The treatment was continued until the disease progressed or an intolerable adverse event occurred (AE). The primary outcome was non-inferiority of OS (non-inferiority margin = 1.08). PFS, TTP, objective response rate (ORR), and safety are secondary goals.

Second-Line Therapy for Advanced HCC

Because sorafenib is the conventional treatment for advanced stage HCC, placebo-controlled comparative trials were done in patients who had progressed on sorafenib or who were intolerant to sorafenib and were unable to continue treatment due to adverse effects.

Up to This Point, There Have Been No Second-Line Trials There were eight placebo-controlled trials of medications such brivanib, everolimus, ramucirumab, S-1,arginine deiminase-conjugated with polyethylene glycol (ADI-PEG20), and tivantinib, but they all failed.[16]

Regorafenib:

Overview of the RESORCE Trial

VEGFR1, VEGFR2, VEGFR3, TIE2, PDGFR, FGFR, KIT, RET, RAF-1, and BRAF are among the protein kinases that regorafenib inhibits. Its molecular structure is nearly identical to that of sorafenib, resulting in a toxicity profile that is extremely similar. It was studied in a phase III placebo-controlled trial in patients who were refractory to sorafenib but not intolerant to it, unlike other medicines. The primary endpoint of OS in the regorafenib arm was significantly superior than the placebo arm (10.6 months vs. 7.8 months). PFS and TTP were also improved significantly. Regorafenib was the first medicine to show efficacy in second-line therapy when compared to placebo. [17]

However, because this medicine is often not suited for treatment in that population, second-line therapy for sorafenib-into-lerant patients remains unfulfilled. The following four elements contributed significantly to the RESORCE trial's success: (1) patients who stopped taking sorafenib due to side effects were excluded from the trial, leaving only patients with PD on sorafenib; (2) imbalances between the active drug and placebo arms were avoided by including vascular invasion and EHS as separate stratification factors; (3) AFP was also included as a stratification factor; and (4) only patients with adequate tolerance to sorafenib (patients able to take at least 400 mg of sorafenib for atleast 20 of the 28 days preceding the PD assessment) were included. This trial design avoided dropouts due to regorafenib side effects and reduced the impact of post-trial regorafenib treatment after PD.

According to the results of the RESORCE trial, median survival time on regorafenib was 10.6 months (placebo: 7.8 months, HR = 0.63, $p < 0.0001$). Moreover, OS subanalysis showed significantly better

results for patients with a Child–Pugh score of 5 on starting sorafenib compared with patients with a score of 6.

Immune Checkpoint Inhibitors

Immune Checkpoints

Professor TasukuHonjo and his research team at Kyoto University in Kyoto, Japan, discovered the immunological checkpoint molecule PD-1 in 1992. When the researchers identified it, they were seeking for chemicals that promoted T lymphocyte apoptosis, thus they dubbed it programmed death-1 (PD-1). [18]

It was later shown to be a receptor that controls immune responses negatively. In the year 2000, the PD-1 ligands PD-L1 and PD-L2 were also identified. After it was recognised that inhibiting this system can kill cancers by reversing the tumor's immunosuppressive effects and restoring innate immune function, anticancer medicines based on that mechanism were developed in 2002.[19]

James Allison identified cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) in 1995 and observed that inhibiting its action caused tumours in mice to vanish. Immunological checkpoint molecules are molecules that govern T lymphocyte activity, and immune checkpoint inhibitors are medications that block these molecules. Anti–PD-1 antibodies nivolumab and pembrolizumab, anti–PD-L1 antibodies avelumab, durvalumab, and atezolizumab, and anti–CTLA-4 antibodies ipilimumab and tremelimumab are now being studied in HCC trials.[20]

Nivolumab

Nivolumab is a human PD-1 monoclonal antibody made from recombinant human IgG4 cells. It produced a response rate of 20% in a phase I/II trial in advanced HCC (Checkmate-040 trial), including two full responses and a disease control rate of 67 percent, which are extremely promising results. Nivolumab's effects also lasted in responders, which was a unique trait. After that, the trial's enrollment was enlarged.The latest results were reported at ASCO 2017, and the OS results were positive, with 28.6 months for first-line therapy and 15.6 months for second-line therapy. A phase III head-to-head trial comparing sorafenib versus placebo is now underway. Because of the above phase I/II study results, the US Food and Drug Administration (FDA) designated nivolumab for priority review, and it was authorised in September 2017. [21]

Pembrolizumab

Pembrolizumab is a recombinant human IgG4 monoclonal antibody against human PD-1, similar to nivolumab. It was tested in a phase II trial for HCC, with results similar to nivolumab, and is now being tested in a placebo-controlled phase III trial as a second-line therapy for patients with HCC that is resistant to or intolerant to sorafenib.[22]

Other Immune Checkpoint Inhibitors

So date, the majority of PD-L1 antibodies in development have only reached phase I or phase II studies. Axitinib and avelumab are being developed together. Bevacizumab and atezolizumab are being developed together. Durvalumab is being tested in combination with tremelimumab, an anti–CTLA-4 antibody. However, as discussed subsequently, these two latter combination medicines have just advanced to phase III studies. Antibodies that block the immunosuppressive checkpoint molecules TIM3 and Lag3 as well as an antibody that promotes the immune stimulatory protein OX40 are in the early stages of development. [23]

Combination Therapy with Immune Checkpoint Inhibitors and Molecular Targeted Agents

Results of an open-label phase *Ib* trial assessing the efficacy and safety of lenvatinib plus pembrolizumab were presented at ESMO 2016. In this trial, which enrolled 13 patients with solid cancers, the therapy yielded a remarkable antitumor effect as demonstrated by the response rate of 69.2% (PR: n = 9, SD: n = 4) and disease control rate of 100% [24]

Though the efficacy of immune checkpoint inhibitors alone has gotten a lot of attention, the efficacy of combination therapy with molecular targeted medicines has gotten a lot of attention as well. Immune checkpoint therapy combined with curative treatment for HCC is also being tested.

Other phase 1b combination therapy are still being tested, such as pembrolizumab plus lenvatinib or SHR 1210 plus aptinib. A phase III trial pitting durvalumab + tremelimumab against sorafenib is also underway. These combination therapy approaches are particularly promising because combining the two medications generates a synergistic effect against the immunosuppressive tumour microenvironment, rather than just an additive effect.[25]

Surveillance after curative intent therapy for HCC

Given the high rate of recurrence after curative purpose surgery for HCC, and the fact that effective salvage or repeat therapy is dependent on finding early disease, patients with HCC are being closely monitored. Intensive surveillance has been shown to increase survival in patients with colorectal cancer who have had curative intent therapy. Intensive surveillance following curative resection for colorectal cancer improves survival, according to a meta-analysis. This is most likely due to the fact that intensive surveillance might detect recurrent disease at an earlier stage. The highest chance to repeat curative intent therapy for recurrent HCC, similar to colorectal cancer liver metastases, is by early diagnosis of the recurring illness.Late recurrences of HCC, rather than true metastatic illness, are assumed to be de novo lesions connected to the underlying chronic liver disease.[26]

CONCLUSION

HCC is a complex disease with a number of risk factors that influence the characteristics of HCC patients, as well as the medications they receive, the course of their condition, and their prognosis. According to recent studies, potentially curative treatments for very early- and early-stage HCC produce excellent results. On the other hand, treatment efficacy for the vast majority of HCC patients urgently has to be improved.

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