Current Standard and Future Perspectives in Non-Surgical Therapy for Hepatocellular Carcinoma

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Keywords

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Abstract

Background: Hepatocellular carcinoma (HCC) is an aggressive liver tumor with a poor 5-year survival rate. Many HCCs are not amenable to surgical resection, because of tumor size, location, or because of the patient's poor liver function, a common obstacle to HCC therapy, because HCCs almost always develop in chronically inflamed livers. **Summary:** In recent years, many efforts have been made to improve patient survival by conducting clinical trials investigating local and systemic treatment options for patients with unresectable tumors. These treatment options include radiofrequency ablation (RFA), transarterial chemoembolization (TACE), selective internal radiotherapy with yttrium-90 (SIRT), stereotactic body radiation therapy (SBRT), proton beam therapy, molecular targeted therapy, and checkpoint inhibition. In this "to-the-point" article, we review the current standard and summarize the most recent findings in unresectable HCC treatment. **Key Points:** (1)

RFA is currently the preferred treatment for patients with tumor burden restricted to the liver and not eligible for surgical resection; (2) TACE is utilized in patients who are not eligible for RFA because of tumor location and/or number of tumor lesions; (3) SIRT might improve treatment responses achieved by TACE and is feasible in patients with portal vein thrombosis; (4) new radiation therapy treatment modalities such as SBRT and proton beam therapy show promising results for local tumor control; and (5) sorafenib remains the first-line systemic treatment option after several large clinical trials have failed to show superiority of other molecular targeted therapies in HCC patients.

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Introduction

Many different treatment modalities exist for non-surgical therapy of non-metastatic hepatocellular carcinomas (HCCs), including interdisciplinary approaches such as local tumor ablation, transarterial embolization (with or without chemotherapy), and radiotherapy. The selection of the appropriate treatment modality for the individual patient is based on several patient specific characteristics, for example, tumor size, location, portal vein thrombosis, and liver function. Assessment of the liver function is particularly important because advanced

cirrhotic liver disease, that is, Child–Pugh score C, is associated with increased therapy-induced toxicity and poor clinical outcome independent of tumor burden. For the treatment of HCC patients with metastatic disease or in whom transarterial embolization failed/is not feasible, the multi-kinase inhibitor sorafenib remains the only approved treatment option for systemic therapy, although several other targeted therapeutic agents have been investigated in clinical trials without proving superior efficacy to sorafenib. In this to-the-point article, we will summarize recent findings and trends in non-surgical therapy of HCC and provide an outlook of future treatment concepts, which are currently being clinically evaluated.

Local Ablation

Radiofrequency ablation (RFA) is the preferred treatment for patients with tumor burden restricted to the liver and not eligible for surgical resection, due to resection criteria or liver dysfunction. Especially in patients with small single tumor lesions, results are excellent and comparable to surgical resection. One study analyzing data from 2 western centers found that patients with a single HCC ≤ 2 cm achieved a median survival of 138 months and a 5-year survival rate of 81%, respectively [1]. Whether these results could be improved by adjuvant sorafenib administration was subsequently investigated. And while data from a retrospective study comparing RFA with adjuvant sorafenib vs. RFA alone revealed a lower incidence of post-RFA recurrence and better overall survival for adjuvant sorafenib in patients with early stage HCC [2], disappointingly, a following phase 3 trial found that sorafenib is not an effective intervention in the adjuvant setting following resection or ablation of HCC [3]. No difference in median recurrence-free survival was observed in patients with or without adjuvant sorafenib treatment. Nevertheless, RFA alone achieves good tumor growth control in patients with small tumor(s) (1–3 tumor nodules ≤ 5 cm) and liver cirrhosis and is thus recommended in practice guidelines as a first-line treatment option in such patients [4].

Transarterial Embolization

For patients with tumor burden restricted to the liver but not eligible for RFA because of tumor location or number of tumor lesions, transarterial chemoembolization (TACE) is the treatment option of choice. Importantly,

a recently published randomized trial investigated the outcome of embolization using microspheres with or without doxorubicin and found no apparent difference between the treatment arms [5]. Thus, while embolization alone (without chemotherapy) is a viable option in an effort to reduce toxicity, transarterial chemotherapy (without embolization) should not be performed [4]. Similar to RFA, sorafenib was also studied in the adjuvant setting following TACE. And as with RFA, no benefit of sorafenib administration post TACE was detected in this phase 2 trial [6]. An important disadvantage of TACE is that patients with portal vein thrombosis are not eligible for this treatment approach. Those patients might benefit from selective internal radiotherapy with yttrium-90 (SIRT). The embolization effects of SIRT compared to TACE are smaller and thus SIRT can be performed on patients with intermediate to advanced HCC and portal vein thrombosis, achieving a time to progression of 7 months [7]. This is a clinically important benefit of SIRT, because portal vein thrombosis is frequently found in patients with HCC, a feature that renders these patients ineligible for TACE. Nevertheless, even when TACE and SIRT are compared irrespective of portal vein thrombosis, SIRT achieves a significantly longer time to progression compared to TACE. Patients in the SIRT group had a median time to progression of >26 months, while patients in the TACE group had a median time to progression of 6.8 months, suggesting that SIRT could reduce the number of drop-outs from liver transplant waiting lists [8]. Future prospective randomized phase 3 trials need to compare SIRT with conventional therapies in order to assess SIRT's place in the treatment of HCC. In summary, transarterial embolization ($\pm$ chemotherapy) and internal radiotherapy are currently indispensable treatment options for patients with HCC.

Radiotherapy

Until recently, radiotherapy was not considered a feasible option for safe treatment of HCC, because both the tumor tissue and the non-tumorous liver tissue are radio-sensitive. However, with technical innovation and the introduction of stereotactic body radiation therapy (SBRT), it is possible to treat tumor tissue with high precision and intensity while sparing surrounding tissue, by delivering high dose radiation to small treatment fields. In a retrospective study analyzing data from 224 HCC patients, SBRT was just as effective as RFA regarding overall 1- and

2-year survival [9]. A different and promising type of radiation therapy, proton therapy, utilizes protons instead of photons (which are used in SBRT) and allows for accurate energy deposition within tumors and safe dose escalation, because of the lack of an exit dose. This is particularly relevant for larger tumors. A phase 2 study of proton beam therapy in patients with localized, unresectable HCC achieved a local control rate of 94.8% at 2 years after treatment initiation [10]. Furthermore, the overall survival rate at 2 years was 63.2% in this study. A major disadvantage of this radiation modality, as of now, is its limited availability. In summary, as with SIRT, further studies are necessary to evaluate SBRT's and proton beam therapy's value in the treatment of HCC.

Targeted Molecular Therapy

To this day, sorafenib remains the only approved drug for systemic treatment of patients with metastatic HCC. It is noteworthy, that a subgroup of HCC patients, carrying VEGFA amplification, has been shown to benefit greatly from sorafenib treatment [11]. Nevertheless, overall improvement of survival through sorafenib administration compared to placebo is modest. Therefore, several large phase 3 clinical trials have been conducted, hoping that newer targeted molecular therapies could alone or in combination with sorafenib surpass sorafenib's anti-tumor efficacy. Unfortunately, these trials had limited success. For example, linifanib was compared to sorafenib in patients with advanced HCC. While time to progression and overall response rate favored linifanib, safety results favored sorafenib; altogether resulting in similar overall survival [12]. Another phase 3 trial found no benefit in adding erlotinib to sorafenib over sorafenib treatment alone [13]. Furthermore, ramucirumab was not effective in the adjuvant setting following sorafenib single agent treatment [14]. More encouraging results come from the phase 3 RESORCE trial, which investigates regorafenib, an oral multi-kinase inhibitor, as a second-line treatment for patients with HCC that progressed after treatment with sorafenib. Patients who received regorafenib had a median overall survival of 10.6 vs. 7.8 months in the placebo group [15]. Another trial with promising results for second-line treatment following sorafenib compared tivantinib, a selective oral MET inhibitor, with placebo in a phase 2 study. In patients with high intratumoral expression of MET, tivantinib improved median time to progression from 1.4 to 2.7 months [16]. If these results are confirmed in phase 3 trials, tivantinib could

become an option for second-line treatment in patients with MET-high tumors. In summary, several molecular targeted therapies proved ineffective in treatment of liver cancer thus far, and only a few have been shown to improve survival, namely sorafenib, regorafenib, and tivantinib. Compared to the effort that has been made in the development and clinical investigation of these molecules, these results are altogether disappointing.

Perspectives

Because of negative results of recent clinical trials investigating molecular targeted therapies for advanced HCC, new treatment approaches are urgently needed. Spontaneous tumor-specific anti-tumor immune responses occur regularly, but they are not capable of containing tumor growth without therapeutic intervention. Checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4, stimulate anti-tumor T cell responses by blocking inhibitory signals that otherwise would restrain T cell function. In patients with advanced HCC, a clinical trial studying anti-PD-1 antibody showed promising results [17]. Eighteen percent of patients had a partial response and 5% had a complete remission, which lasted 14–17+ months. In line with these results were findings from our own trial, in which we investigated tremelimumab, an anti-CTLA-4 antibody, in combination with TACE or RFA [18]. The rationale for this combinatorial treatment approach was that local ablative therapies are known to induce anti-tumor immune responses through antigen release of dying tumor cells, which might synergize with T cell stimulation through checkpoint inhibition. A total of 26.3% of patients achieved partial response in lesions that were not treated directly with ablation, and the median overall survival of all patients in this heavily pretreated cohort was 12.3 months. These data warrant further investigation of checkpoint inhibitors in treatment of HCC in larger clinical trials. Still, as with molecular targeted therapies, only a minority of patients respond to these immunotherapeutic treatment approaches. It is important to note, that HCCs are genomically heterogeneous, with distinct oncogenic mutations, causing activation of different oncogenic pathways in different patients. This might explain, at least in part, why molecular targeted therapies improve survival of patients only modestly overall (see above), when no patient stratification is performed, and why only some patients respond to checkpoint inhibition, albeit with profound responses.

Thus, knowledge about the aberrantly activated signaling pathways in HCC prior to initiation of therapy should inform decision-making and ultimately lead to personalized treatment approaches of patients with HCC.

Key Points

1. RFA is currently the preferred treatment for patients with tumor burden restricted to the liver and not eligible for surgical resection.
2. TACE is utilized in patients who are not eligible for RFA because of tumor location and/or number of tumor lesions.

3. SIRT might improve treatment responses achieved by TACE and is feasible in patients with portal vein thrombosis.
4. New radiation therapy treatment modalities such as SBRT and proton beam therapy show promising results for local tumor control.
5. Sorafenib remains the first-line systemic treatment option after several large clinical trials have failed to show superiority of other molecular targeted therapies in HCC patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

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