New Developments in the Treatment of Hepatocellular Carcinoma: The Concept of Adjuvant and Neoadjuvant Chemotherapy

Hepatocellular carcinoma (HCC) is the commonest liver malignancy, and its annual incidence has been estimated to be 2.8 per 100,000 population in India.[1] There is evidence to suggest that the incidence and prevalence of HCC are rising because of the raging epidemic of nonalcoholic fatty liver disease, and the condition is likely to become the leading cause of cancer in India in near future.[2] The situation is similar in the Western world too.[3] The prognosis of HCC is dismal because of several reasons. Most cases in India are diagnosed at an advanced stage (BCLC-A: 13%; BCLC-B: 39%; BCLC-C 23%; BCLC-D: 13%).[4] Moreover, the curative treatments are often out of the economic reach of an average man.

A conventional oncological approach (with systemic chemotherapy, external radiotherapy, or plain surgery) does not work for HCC because of associated cirrhosis and portal hypertension in most patients. Therefore, a wide range of new approaches, ranging from drastic to minimally invasive ones, were tried and soon became popular. These include treatment with curative intent such as liver transplantation (LT), resection or ablative techniques (such as percutaneous radiofrequency ablation [RFA], percutaneous ethanol injection, microwave ablation [MWA], cryoablation [CA], irreversible electroporation) in early stages of HCC (BCLC-0 and BCLC-A). In addition, one also has locoregional treatments with palliative intent such as transarterial chemoembolization (TACE) or chemoembolization with drug-eluting beads and, more recently, local endovascular radiotherapy via transarterial delivery of beta-emitting microparticles (selective internal radiation therapy) for later stages of HCC (BCLC-B and BCLC-C).[5] Attempts have also been made to downstage the incurable or late-stage tumors to make them amenable to curative treatment.[6] Thus, treatment of HCC remains complex and enigmatic.

In this issue of the journal, there are two reports concerning the treatment of HCC. Kedarisetty et al[7] have described a prospective, single-center experience with treatment of 112 patients with HCC treated with TACE. They have shown that early initiation of N-acetyl cysteine in those with post-TACE embolization syndrome reduces the transaminase level significantly. It is basically a proof-of-concept study for use of N-acetyl cysteine in post-TACE transaminitis, although the period of hospitalization was not different with this treatment. On the other hand, Kalra et al[8] have reported the initial experience with percutaneous CA for early-stage liver tumors. Technical success was achieved in all 9 patients. Complete response was achieved in 7 (77.8%) patients. There was no local tumor progression and no death during the median follow-up period of 7 months. There was no procedure-related complication. The study demonstrates the feasibility and safety of this ablative technique; however, no attempt has been made to compare it with the more popular RFA. In the succeeding paragraphs, the changing approach to locoregional therapies in overall management of HCC in the wake of new developments is briefly reviewed.

Firstly, there is a rich experience of using heat-based tumor ablation therapies such as RFA and MWA, but experience with freezing the tumor tissue is relatively limited.[9] RFA has technical limitations such as impedance from charred tissue and relative tissue susceptibility to heat sink effects. CA causes cell damage by freezing intracellular and extracellular fluid and subsequent cell death.[10] CA has the advantage of reduced rates of gallbladder or bowel injury and less painful procedure in superficial lesions, although relatively longer freezing times, as well as the need for multiple cryoprobes, may be cited as a limitation.[11] CA may be the modality of choice when precision is needed for tumors near vulnerable structures such as blood vessels because the ablation zone can be monitored in real time on intraprocedural computed tomography. A lot more needs to be learned about relative merits of various ablative treatments in HCC.

Second, TACE remains the most widely available and popular therapy for intermediate-stage HCC and is well supported by evidence.[12] There is robust evidence that TACE can prolong life in BCLC stage B, but it is considered a palliative treatment. TACE sessions when repeated over time lead to progressive deterioration of liver function, making patients unfit later even for systemic therapy.[13] Deteriorating liver functions also significantly reduce the survival benefits of systemic therapy. Therefore, the optimum timing for giving up TACE and starting systemic therapy has been a matter of debate, and various scores have been developed to have clearer guidelines with limited benefit.[14,15] It has been suggested that the hypoxic environment created by the TACE procedure stimulates induction of vascular endothelial growth

Abbreviations: CA: Cryoablation; HCC: Hepatocellular carcinoma; ICI: Immune checkpoint inhibitor; LT: Liver transplantation; MKI: Multikinase inhibitor; MWA: Microwave ablation; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization

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factor (VEGF) and other angiogenic pathways, promoting revascularization, neoangiogenesis, and growth of the residual viable tumor.[16,17]

Third, exciting developments have taken place on the systemic therapy front. The development of the molecular-targeted agent sorafenib that improved survival in late-stage HCC is old news now.[18] In the last 3–4 years, a series of new drugs have become available for clinical use, which are as good as or even better than sorafenib and work through several mechanisms including inhibition of angiogenesis.[19–21] Another recent trial (IMbrave150)[22] demonstrated that atezolizumab plus bevacizumab improves overall survival and all other efficacy outcomes when compared with those obtained with sorafenib monotherapy.

COMBINATIONS

Time was now ripe to combine locoregional therapies with systemic therapies to see if one can achieve a miraculous summation of results.[23,24] Several schedules were tried aiming to minimize the angiogenic upsurge induced by TACE and to maximize synergy.[12] Initial attempts to combine TACE with sorafenib failed to show exciting results.[25] However, some studies confirmed the feasibility and demonstrated a positive effect on survival in BCLC stage C disease.[12] Because many of these were retrospective analyses, the results were not particularly convincing.[26] Use of drugs other than sorafenib, for example, thalidomide, bevacizumab, and brivanib did not change the outcome much. However, more recently, a prospective study, the "TACTICS trial" has shown highly promising results.[27] It has been shown that TACE plus sorafenib in patients with unresectable HCC significantly improved PFS over TACE alone.

Combining TACE with immunotherapy is also an attractive option. LRT on its own can drive antitumor immune responses as it can release tumor antigens (DAMPs), activate the innate immune system, and generate sustained T-cell immunity. It can also lead to checkpoint blockade to maintain T-cell effector function. Patients treated with TACE show greater TAA-specific CD8+ T-cell responses. One can hypothesize that CPI therapy given in a highly immunogenic environment will increase the chance of overcoming local tumor-mediated immune suppression.[12,28] Replacing TACE with other locoregional therapies such as TARE is also an interesting option. LRT is also used to downstage HCC beyond Milan criteria to consider the curative option of LT in patients with the intermediate-stage disease. Whether combination therapies can make downstaging more efficient remains to be seen.

NEOADJUVANT THERAPIES

There is a compelling argument to use systemic therapy before rather than after tumor ablation or surgery. In animal models, it has been shown that immunotherapy could improve survival if the primary tumor was in situ as it leads to enhanced tumor-specific CD8+ T-cell activation.[29] Thus, immunotherapy before tumor resection can induce an effect like a vaccine, resulting in sustained systemic immune surveillance.[30] Several other studies have also shown that systemic therapy in the neoadjuvant setting leads to enhanced therapeutic benefit by adequate maturing of Baft3+ dendritic cells (which are the most potent cross-

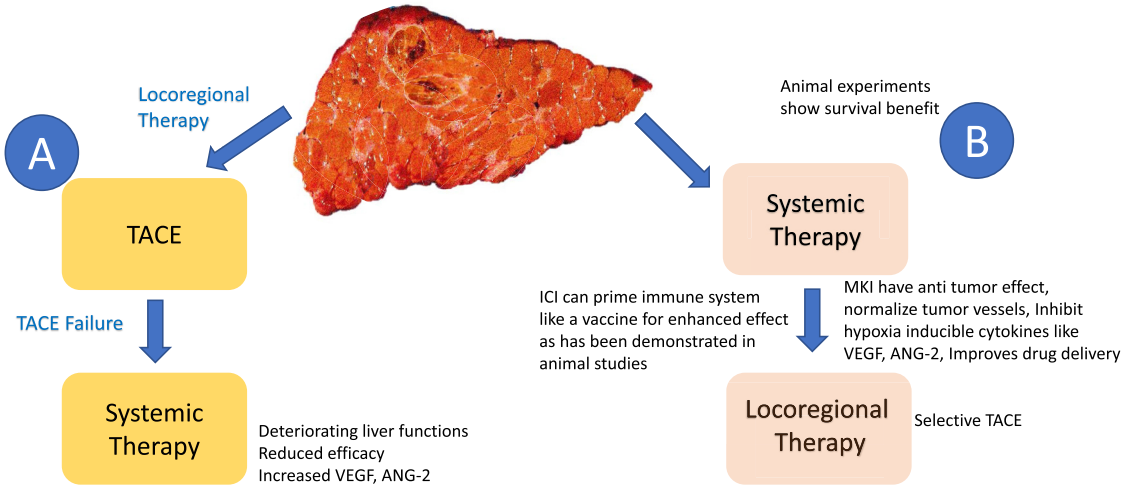

Figure 1 Two approaches for combining systemic therapy with locoregional therapy. The conventional approach (A) is to give systemic therapy if TACE fails. Many patients would have deterioration in liver functions, which would make the patient ineligible for systemic therapy or make it less effective. The neoadjuvant approach (B) offers several theoretical advantages. It has shown better response rates in experimental models and in human tumors other than HCC. Drugs such as lenvatinib can also inhibit hypoxia-induced angiogenesis after TACE. HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization; ICI: immune checkpoint inhibitor; VEGF: vascular endothelial growth factor; ANG-2: angiopoietin-2; MKI: multikinase inhibitors.

presenters of TAA to CD8+ T cells) and by stimulating immune-exhausted tumor-infiltrating lymphocytes, expansion of Tcf1+ PD-1+ stem–like subsets, and proliferation of subdominant T-cell clones.[30–32] There is also evidence to show that a certain period of time is crucial between use of immunotherapy and surgery among metastatic mouse tumor models as IFN-γ secretion from tumor antigen–specific T cells may be affected.[33]

Evidence is accumulating that use of immune checkpoint inhibitors (ICIs) as a neoadjuvant therapy in tumors other than HCC (e.g., melanoma, lung cancer, bladder cancer, head and neck squamous cell carcinoma, and so on)[12,34–36] gives higher response rates, although larger studies are needed to confirm these findings. Neoadjuvant studies indicate that the peak benefit of this therapy may be seen within the first week.[37] It is interesting to note that in a subset of patients, tumors can undergo significant downstaging within a short period of time, which may permit less morbid resection.[38] However, the adverse effects of currently available therapies remain a major limiting factor.[39]

The concept of neoadjuvant immunotherapy, if proven, will be beneficial even for patients being treated with a curative intent by resection and ablation. Such patients presently have higher risk of recurrence than LT.[40,41] The risk factors of such a high recurrence are well known, and such patients may be the candidate for neoadjuvant therapy.[42] Preliminary data have suggested that the neoadjuvant approach to downstage may be feasible in intrahepatic cholangiocarcinoma.[43] Similar innovative approaches with systemic therapy upfront in intermediate-stage HCC followed by TACE are also being tried.[44] It is presumed that a multikinase inhibitor such as lenvatinib, if given early, may exert an antitumor effect, normalize tumor vessels, and improve drug delivery. Lenvatinib will also inhibit hypoxia-inducible cytokines such as VEGF and angiopoietin-2 later when TACE is given subsequently (see Figure 1). Finally, with the development of a new ICI for HCC, its neoadjuvant use may become a preferred choice before other forms of therapy soon. A fair number of trials of such combination therapy both in the advanced-stage HCC and in the early- and intermediate-stage HCC are underway.[45]

HCC

CONFLICTS OF INTEREST

The authors have none to declare.

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