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REVIEW

Locoregional therapy in hepatocellular carcinoma: when to start and when to stop and when to revisit

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With increasing therapeutic options available for advanced hepatocellular carcinoma (HCC), the timing and sequencing of locoregional and systemic therapy need to be re-examined. This is especially so for patients with intermediate HCC, so as to optimize responses while preserving liver reserves, and in so allowing our patients to achieve the best survival outcomes possible.

Key words: hepatocellular carcinoma, locoregional therapy, systemic therapy, sequencing of therapy

INTRODUCTION

In many regional and global guidelines on the management of hepatocellular carcinoma (HCC), locoregional therapy is listed as the preferred option for unresectable Barcelona Clinic Liver Cancer (BCLC) A and B disease, while systemic therapy is the recommended choice for BCLC C HCC.[1,2]

In recent years, there has been an increasing number of systemic therapy options for unresectable HCC. Many of these options offer higher disease control rates but their real-world applicability is often limited by the patients' underlying liver function. Patients with intermediate HCC also form a heterogeneous group and recommendations may have to be tailored for an individual's disease and clinical characteristics.

It is hence important to re-examine the traditional linear mindset of transiting to systemic options only when locoregional options are exhausted, especially relevant for patients with intermediate HCC, so as to better optimize their outcomes.

HETEROGENEITY IN INTERMEDIATE HEPATOCELLULAR CARCINOMA

Patients with intermediate HCC can differ widely in terms of their liver function, tumour size, and tumour number.[3] Despite this heterogeneity, however, transarterial chemotherapy (TACE) is currently the standard recommendation by most international guidelines for this group of patients.[1,2]

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The optimal treatment for each patient in this group, however, should be the treatment that accords a high response rate while best allowing preservation of liver function—and the modality which allows this may differ depending on the individual's cancer characteristics and liver function.

Ablative techniques

Ablative techniques can be considered for patients with early HCC or low-volume intermediate HCC. The most common ablative technique used is radiofrequency ablation (RFA). RFA is most efficacious for small-volume disease and can yield similar survival outcomes compared with surgical resection for small lesions <2 cm.[4] RFA is best indicated for lesions <3 cm, which more likely to achieve complete necrosis. Ablating larger lesions is more likely to leave residual tumour, with only 45% of tumours >5 cm achieving complete necrosis after RFA, compared with 90% in tumours <3 cm.[5]

Microwave ablation and cryoablation are other ablative techniques that can also be considered and may be better to better achieve complete tumour ablation in larger tumours.[6]

In patients with inoperable HCC, stereotactic body radiation therapy can also be an alternative to RFA for local treatment, and may even be associated with better outcomes for tumours >2 cm.[7] Stereotactic body radiation therapy has also been used as a bridge to liver transplantation, and may be as effective as TACE or RFA for this purpose.[8,9]

Transarterial chemotherapy

The benefit of TACE was demonstrated in a meta-analysis of seven randomized controlled trials demonstrating survival benefit over best supportive care in patients with

intermediate HCC.[10] While there is no universal agreement on the type or dose of chemotherapy used or the exact conventional TACE (cTACE) method, TACE with fixed dose drug-eluting beads (DEB-TACE) has been studied. In the PRECISION V randomized phase II trial comparing cTACE with DEB-TACE with doxorubicin, DEB-TACE was associated with a numerically higher response rate and disease control rate, though this did not reach statistical significance. DEB-TACE was, however, superior in achieving lower liver and cardiac toxicity rates.[11] A subsequent meta-analysis of several trials, however, was unable to corroborate superiority for survival outcomes or toxicity profile for DEB-TACE over cTACE,[12] and both DEB-TACE and cTACE are still carried out, often according to institutional preferences.

Outcomes in reported literature for patients undergoing TACE are heterogeneous and this is likely related at least in part to the differences in selection of patient suitability for the procedure.[13] In a trial of patients with unresectable HCC randomized to receive arterial embolization or chemoembolization compared with conservative treatment, the ability to achieve a sustained response for at least 6 months was shown to be an independent predictor of survival, while nonresponders and the control group had no differences in survival.[14] A large retrospective analysis from Japan showed that the ability to deliver selective, rather than nonselective, chemoembolization was also associated with better survival in a multivariate Cox model.[15] These two studies underscore the principle that TACE achieves the best outcomes in a select group of patients.

Several prognostic scores have been developed to help clinicians decide on which patients are most likely to benefit from the procedure,[16-18] the most widely validated being the HAP (Hepatoma Arterial-Embolization Prognostic) Score[16,19] which aims to predict survival in patients who are planned for TACE by considering baseline liver function, tumour extent and alpha fetoprotein levels. However, there is no universally agreed scoring system for TACE patient selection,[20] and a multidisciplinary discussion is often the best approach.

Transarterial radioembolization or selective internal radiation therapy

Selective internal radiation therapy (SIRT) is another transarterial locoregional therapy that can be considered for HCC, in which microspheres coated with radioactive isotopes are introduced intra-arterially into the tumour-feeding vessels. SIRT has been used as a bridge to liver transplantation.[21] In a phase II trial comparing TACE with SIRT in BCLC A/B HCC, the latter resulted in better time to treatment progression than TACE and less drop out from the transplant waiting list.[22] In inoperable intermediate HCC, however, two large randomized controlled trials comparing SIRT with sorafenib did not show an improved overall survival or progression-free survival with SIRT.[23,24] SIRT though was associated with a higher overall response rate of ~16%-20% and a better toxicity profile. In the ESMO guidelines, SIRT can be considered as an option for patients with liver-limited disease and preserved liver function in whom neither TACE nor systemic therapy is possible, or for use as a bridging therapy to liver transplant.[1]

Combining locoregional therapy with systemic therapy

In the near future, this field will evolve further with the combination of locoregional therapy and systemic therapy. Earlier trials which combined targeted therapies with TACE did not show survival benefit compared with TACE on its own,[25-27] whereas the TACTICS trial did show progression-free survival improvement when sorafenib was given 2-3 weeks before first TACE in well-selected HCC patients.

With the advent of immunotherapy, the combinatorial approach has gained more attention, purportedly on the hypotheses of cell death induction by locoregional methods increasing tumour immunogenicity, and hence locoregional therapies may be synergistic when combined with immune-checkpoint inhibitors.[28]

Two of these trials, evaluating the combination of SIRT with the anti-PD1 inhibitor nivolumab,[29,30] have been completed and presented in part, and show promising disease control rates of 60%-80%, with manageable safety profiles. Various other combination strategies are also being studied, including SIRT with atezolizumab—bevacizumab (NCT04541173), TACE with durvalumab—bevacizumab (NCT03778957) among many others.

Systemic therapies for intermediate HCC

With increasing and more effective systemic options,[31,32] there is also more interest in introducing these therapies earlier in disease course, challenging the traditional treatment paradigm of turning to systemic therapies only when locoregional therapies are exhausted. Overexposing patients to locoregional therapies may not only be ineffective but may also risk deterioration of liver function. Sequential exposure to systemic therapies is contingent on intact liver function and is associated with improved survival outcomes.[33]

Deciding when to switch from locoregional to systemic therapy in intermediate HCC

While locoregional therapy is still the standard of care for intermediate HCC, conferring good outcomes for many patients, the optimal therapy for this group of patients continues to evolve with advances made in systemic therapy. We need to be more selective of who should continue locoregional therapy, taking into consideration patient's liver function, extent and biology of disease; prior response to locoregional therapy and other factors that will ensure maintenance of patient's liver function.

For TACE, there have been several scores to help the clinician assess the suitability of continuing with another TACE procedure, such as the ART (Assessment for Retreatment with TACE) score[34] and the ABCR score.[35] Both scores take into account several factors, such as liver function and prior radiological response to assess suitability for retreatment with TACE. While these scores are prognostic, they

require prospective validation before they can be used routinely in clinical practice.

The ability to select patients who are more likely to respond favourably to TACE, in terms of both tumour response and preservation of liver function, cannot be emphasized enough as HCC patients are often dealing with two issues simultaneously, namely, that of the cancer and of underlying liver cirrhosis. In real-world practice, TACE is likely overutilized beyond guideline recommendations, and can result in liver dysfunction. In the international observational study OPTIMIS, 39% of patients received TACE despite being ineligible for the procedure according to practice guidelines.[36] This is especially important given that 11%-20% of patients experience deterioration in liver function after the procedure. Subjecting them to locoregional therapies in these scenarios may hence not only be inefficacious, but also potentially detrimental and limit their ability to receive subsequent effective therapies. Retrospective studies in Japan have shown that in TACE refractory patients, switch to systemic therapy such as sorafenib may improve survival outcomes compared with continuing with further ineffective TACE.[37,38] This may at least be in part due to the preservation of liver function, allowing patients to undergo sequential systemic therapy and hence achieving better outcomes.[33] There are also scoring systems aside from the Child—Pugh score which have been proposed to have better assessment of liver function. These include the Albumin—Bilirubin (ALBI) grade and its variants, which have been shown in several series to have improved predictive value of benefit after locoregional therapy,[39,40] and may allow us to better select those who can maintain liver function after TACE and other locoregional treatments.

In Asia, the Japan Society of Hepatology (JSH) defined the criteria for TACE refractoriness/failure as follows: if there are two or more ineffective responses seen within the treated tumours, two or more consecutive progressions in the liver, continuous elevation of tumour markers, appearance of vascular invasion or extrahepatic spread.[41] Similarly in the West, algorithms have been proposed to try to better define and limit the use of TACE, including one by Raoul et al.[42]

Aside from determining what constitutes TACE refractoriness, it is also important to identify patients who are TACE unsuitable. This was the subject of the 2019 Asia-Pacific Primary Liver Cancer Expert (APPLE) consensus statement, which attempted to define a group of intermediate HCC patients in whom TACE is not necessarily technically unfeasible, but may be biologically unsuitable.[2] This may be related to the presence of characteristics suggesting (i) unlikeliness to response to TACE: confluent multinodular disease, massive or infiltrative disease, simple nodular type with extranodular growth, poorly differentiated histology, intrahepatic multiple disseminated nodules or sarcomatous changes after prior TACE; (ii) likely to develop TACE failure/refractoriness: based on up-to-7 criteria; or (iii) likely to become Child—Pugh B or C after TACE: modified ALBI grade 2b. In these patients, earlier usage of systemic therapy, particularly options with high response rates, may be preferred to proceeding with locoregional therapies and risking interim deterioration of liver function. Of note, while this consensus may not be universally accepted, it underlines the need to be more selective when TACE is considered for patients with intermediate HCC.

Revisiting locoregional therapy after systemic therapy

The high response rates with newer systemic regimens can also be used to challenge the traditional treatment paradigm. Patients deemed unlikely to respond to upfront locoregional therapy may benefit from the high response rates with newer systemic therapy options instead, with locoregional therapy applied on-demand either to consolidate response or to address refractory lesions. The traditional one-way transition from locoregional options to systemic options on disease progression hence needs to be also re-examined. Revisiting the use of locoregional options is an important strategy in patients with response to systemic therapies.

In Japan, a proof-of-concept retrospective study comparing lenvatinib versus TACE as initial treatment in patients with intermediate-stage HCC beyond up-to-7 criteria showed better overall survival and lesser deterioration in liver function among patients given upfront lenvatinib.[43] Aside from lenvatinib, the sequencing of other systemic therapy options with high response rates, such as the atezolizumab—bevacizumab combination (NCT04224636), with respect to locoregional therapy is also under investigation.

CONCLUSIONS

Locoregional therapies such as RFA and TACE are effective treatments for selected localized HCCs and still have an important place in the treatment of HCC. A key component to ensuring good outcomes in patients with HCC is maintenance of good liver function. There is a need to better refine patient selection for locoregional therapies in order to achieve better outcomes. This may involve validating subclassifications of intermediate HCC and/or developing better predictive biomarkers for therapy. In addition, with the advent of more effective systemic therapies, the decision to stop locoregional therapy and switch to systemic therapy is evolving and has to be individualized to the patient's situation. Studies need to be carried out to address the optimal treatment algorithm for transitioning from locoregional to systemic therapy and vice versa. It remains to be seen whether combination approaches with systemic and locoregional therapies will result in further paradigm shifts.

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