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REVIEW

Neoadjuvant Therapy for Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is characterized by low resection and high postoperative recurrence rates, and conventional treatment strategies have failed to meet clinical needs. Neoadjuvant therapy (NAT) is widely employed in the routine management of several solid tumors because it increases resectability and reduces the rate of postoperative recurrence. However, a consensus has not been reached regarding the effects of NAT on HCC. As systemic therapy, particularly targeted therapy and immunotherapy, is given for HCC treatment, accumulating evidence shows that the "spring" of NAT for HCC is imminent. In the future, HCC researchers should focus on identifying biomarkers for treatment response, explore the mechanisms of resistance, and standardize the endpoints of NAT.

Keywords: neoadjuvant therapy, hepatocellular carcinoma, HCC, immunotherapy, systemic therapy, chemotherapy

Introduction

Neoadjuvant therapy (NAT) is the administration of therapeutic agents prior to definitive Surgery.[1,2] It was first applied in cancer a half century ago. In 1955, Pisani et al first attempted to treat breast cancer with neoadjuvant radiotherapy (RT).[3,4] Neoadjuvant chemotherapy (NAC) was then introduced in breast cancer treatment in 1985.[5,6] At the same time as Pisani, neoadjuvant RT was introduced in colorectal cancer treatment by Stearns et al[7,8] In 1986, Smith et al administered combined preoperative neoadjuvant RT and chemotherapy for anal and rectal cancer.[9] Since the 1990s, an increasing number of patients with solid tumors, such as lung, ovarian, prostate, esophageal, and gastric cancers, have been treated with NAT, and they have achieved remarkable outcomes, including significant improvement in survival time and quality of life.[10–18] This subverts the belief that surgery is the only curative treatment for tumors or that surgery should be the first consideration. Currently, it is unclear why these tumors benefit from NAT, but consensus has been established that NAT is an important part of the treatment of the aforementioned cancers[19,20] (Figure 1).

In contrast to the aforementioned tumors, no convincing evidence of the effectiveness of NAT in hepatocellular carcinoma (HCC) has been reported for a long period of time.[21–24] Among cancers, HCC consistently ranks high in terms of morbidity and mortality rates.[25,26] More than 20% of patients who are initially eligible for liver transplantation (LT) drop out before transplantation due to tumor progression.[27,28] Although considerable progress has been made in perioperative management and postoperative therapies, no significant improvement has been observed in postoperative 5-year overall survival (OS) rate and recurrence rate in patients with HCC.[26,29–33] Thus, some preoperative interventions may be feasible methods to improve the prognosis of patients.[34] This review provides an overview of the development of NATs and discusses how these various types of NATs can be used to downstage the tumor and increase the resectability of HCC. Articles were identified through a search of PubMed with the search terms "neoadjuvant radiotherapy", "neoadjuvant chemotherapy", "immunotherapy", "neoadjuvant therapy", "ablation therapy", "systemic therapy", "target therapy", "hepatocellular carcinoma", and "HCC" from 1950 until

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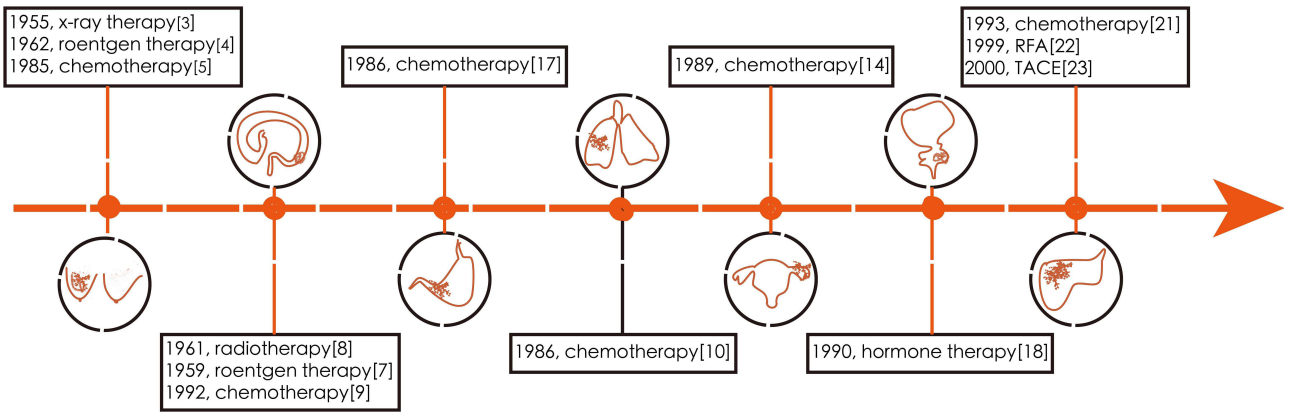

Figure 1 Timeline of the application of NAT in cancers. Neoadjuvant therapy (NAT) has a long history of being used in the treatment of solid tumors. The commonly used types of NAT are radiotherapy, hormone therapy, chemotherapy, and physical energy therapy. In the 1990s, the outcomes of the initial application of NAT in the treatment of HCC were not satisfactory, leading to absence of large scale application of NAT in HCC treatment.

July 2021. Only papers published in English were reviewed. The final list of articles was generated on the basis of originality and relevance to the broad scope of this review.

Rationale of NAT for HCC

Unlike other organs, the liver has a complex anatomical structure. Various antigens from the digestive tract, such as gut nutrients, toxins, and metabolites, move into the bloodstream, and thus, the liver contains many immune cells, which confers the liver with high tolerance for immune function. Different compositions of immune cells have been observed in the immune microenvironment of primary and recurrent tumors.[35] The relatively high tolerance threshold of the liver immune microenvironment facilitates immune escape during tumor development.[36–41] Hence, the liver is widely considered as an immune organ.[42] Additionally, compared with well-differentiated organs, the liver has renewable function. Even in adulthood, some pluripotent stem cells exist in various parts of the liver.[43] Because of the presence of these cells, liver cancer exhibits strong temporal and spatial heterogeneity.[44,45] Different clonal types are present in the same HCC lesion, and they progress over time according to different clonal patterns.[46] The genomic and epigenomic expression profiles in the early and late disease stages are very different, even in the same tumor lesion.[46–48] Many signaling pathways are involved in the occurrence and development of HCC. For example, vascular endothelial growth factor (VEGF) and VEGF receptor and platelet-derived growth factor receptor/fibroblast growth factor receptor (PDGFR/FGFR) participate in tumor angiogenesis and maintenance of mature blood vessels.[49] EGFR/ IGF/ HGF/ e-MET, PI3K/ AKT/ mTOR, RAS/ RAF/ MEK/ ERK, and other signaling pathways are involved in tumor cell proliferation, motility, and apoptosis inhibition.[50–52] According to recent molecular biology-related evidence, HCC can be categorized into many subtypes, eg, metabolism-driven, micro-environmental imbalance, and proliferation-driven subtypes.[31,53] Different subtypes correspond to different therapeutic drugs or methods, which lead to significant differences in the prognosis of patients with HCC.[53–56] The liver is the primary target organ for hepatitis viruses and harmful substances, such as alcohol. Long-term chronic interactions between liver cells and harmful agents lead to liver fibrosis and even cirrhotic nodules. These pathological structural changes will affect the physiological function of the liver; however, they will also affect drugs for liver cancer as they enter the target organ to kill cancer cells or activate the immune system to exert antitumor effects[36,46,54,56,57] (Figure 2).

NAT for HCC

Similar to the role of NAT in other tumors, the application of NAT in HCC has many advantages and potential benefits. First, surgery may be allowed in patients with insufficient residual liver volume following NAT. Approximately 60% of patients with HCC have large tumors or tumor lesions that are distributed within multiple liver lobes at diagnosis.[31,44] It is difficult for these patients to have sufficient residual liver volume (~30%) to support postoperative recovery (eg,

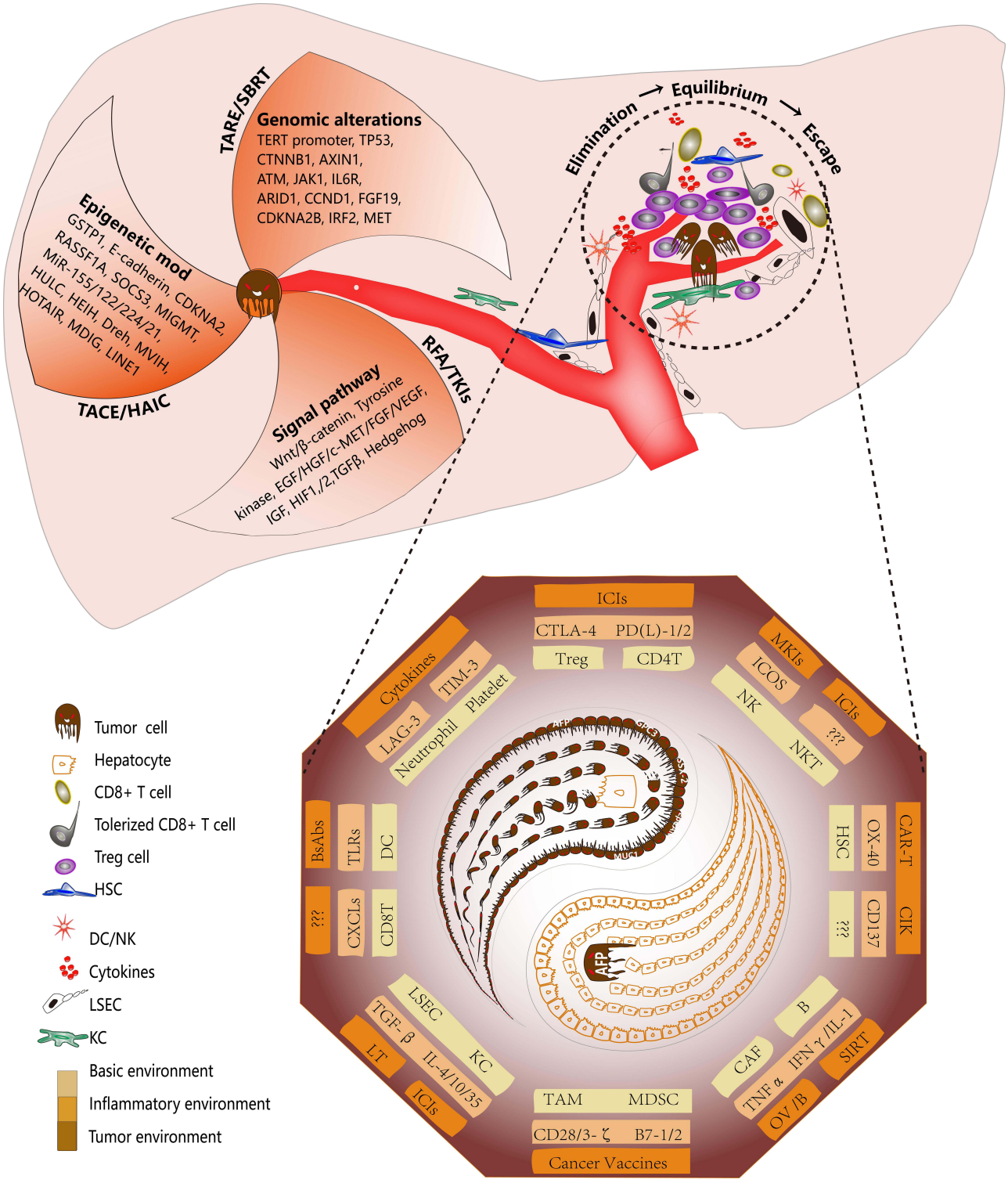

Figure 2 Diagram showing the rationale for NAT in HCC. The occurrence and development of HCC are driven by intrinsic and extrinsic factors. The intrinsic factors include genomic alterations, epigenetic modifications, and abnormal regulation of cell signaling pathways. For these factors, targeted agents, adeno-associated virus-driven gene editing, DNA methyltransferases, and histone deacetylases are being investigated in a NAT setting for HCC. The extrinsic factors primarily comprise interactions between the tumor immune microenvironment and cancer cells. Progression involves three stages. During the elimination stage, tumor neoantigens elicit an immune response that eliminates most malignant cells. During the equilibrium stage, tumor cells with neoantigens that are incapable of inducing an immune response or that have acquired the ability to evade the immune system survive and proliferate. During the escape stage, tumor cells escape immunosurveillance and lead to the development of an immunosuppressed environment. For the target site of the immune cells, an increasing number of agents, such as those that target PD-1/PD-L1, cytotoxic T-lymphocyte antigen 4 (CTLA-4), TGF-β, and TIM-3, have been explored as NATs for HCC.

extended right hemi-hepatectomy). Currently, the only method suitable for these patients is associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), but the scope for application of this procedure is very limited.[58–60] Second, NAT increases safety during the perioperative period. Large tumors, especially those at specific locations, often compress or invade important intrahepatic structures, such as the portal vein or bile ducts. This increases the difficulty of radical resection of liver tumors and the timing of surgery, and consequently, leads to an increased incidence of surgical complications and delays in the application of adjuvant therapy.[61,62] These perioperative factors may undermine the potential benefits of the surgery. Third, NAT predicts anticancer drug sensitivity. After locoregional therapies, such as transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), or surgery, the margins of liver tumors are significantly damaged, making it difficult to accurately evaluate the efficacy of anticancer drugs based on current detection methods (computed tomography or magnetic resonance imaging). However, NAT, especially neoadjuvant drug therapy, can be used to accurately evaluate the sensitivity of tumors to anticancer drugs in a relatively short time. This also provides some reference for adjuvant therapy in patients with HCC. Fourth, NAT might be an option to reduce the risk of early recurrences. HCC usually occurs as a multiclonal cancer. Preoperatively, tumor cells may have already migrated into the liver and the surrounding region.[63] If only the macroscopic and visible tumor tissues are surgically removed, the patient will likely experience early postoperative recurrence. This somewhat explains why the early recurrence rate in patients with HCC is 70% postoperatively. This was also confirmed by differences in the early recurrence rate between patients with HCC who underwent partial hepatectomy and those who underwent LT.[61,62,64] For microsatellite lesions, NAT achieves full contact between anticancer drugs and tumor cells, or alternatively, NAT changes the immune microenvironment of the lesions to maximize the tumor-killing effect, thereby reducing the risk of early postoperative recurrence. Briefly, NAT could be useful to downstage HCC to enable optimal surgical resection or to meet the criteria for liver resection (LR), which will lead to the improved prognosis of patients with HCC.

NAC

Similar to the role of NAT in other tumors, NAC was the first regimen investigated as a NAT for HCC. In 1989, Marvin et al treated three patients with unresectable HCC with the cytotoxic drug doxorubicin.[65] Four years later, the same group conducted a pilot study comprising 20 patients.[21] They concluded that neoadjuvant doxorubicin chemotherapy favorably alters the post-transplant survival of patients with HCC.[21] Encouraged by their findings, more researchers treated patients with HCC with NAC.[66–68] To reduce the systemic side effects of chemotherapy, TACE and hepatic arterial infusion chemotherapy (HAIC) were developed as alternatives to systemic chemotherapy.[68–72] Chemotherapeutic drugs such as mitomycin, epirubicin, and cisplatin were delivered to the tumor site in high concentrations and were continuously administered through a tumor feeding artery. Most chemotherapeutic drugs are dose-dependent, and thus, locoregional administration enhances their killing effect on tumors.[73–75] Tumors initially exceeding the Milan Criteria (MC) that were treated with neoadjuvant TACE achieved a post-transplant 5-year survival rate and HCC recurrence-free probability equal to those of patients with tumors within the MC.[76] Among patients with advanced, Child–Pugh class A HCC, 11.7% were down staged to hepatectomy after neoadjuvant HAIC for 3 months.[77] Neoadjuvant TACE was significantly associated with improved OS and recurrence-free survival after LR of large HCC tumors (≥10 cm).[78,79] Additionally, TACE or HAIC combined with RT could serve as an alternative for a subset of patients with advanced HCC. Hepatectomy after downstaging by three-dimensional conformal RT combined with HAIC was safe and resulted in good long-term outcomes.[80] For patients with portal vein tumor thrombosis (PVTT), a 26.5% resection rate and 100% response rate were recorded after downstaging with localized concurrent chemoradiotherapy (CCRT) followed by HAIC.[81] The disease-specific survival rate differed significantly between patients who underwent resection after localized CCRT and those who underwent resection first (median, 62 months vs 15 months).[81] For resectable HCCs, including small HCCs, a retrospective study that compared 1725 patients found that effective neoadjuvant TACE led to a 5-year disease-free survival rate of 56.8%, which was superior to that after surgical resection alone.[82] However, some studies did not support the use of TACE/HAIC as NATs for HCC.[78,83–87] Presently, clinicians have not reached a consensus. The establishment of an effective prognostic model and the accurate distinction of patients who are suitable for neoadjuvant TACE/HAIC are keys to promoting these strategies in clinical practice.[85,88,89]

Neoadjuvant RT

RT comprises external and internal RT and plays an increasingly important role in HCC treatment. The universal application of external RT includes stereotactic body RT (SBRT), 3-DCRT, and intensity-modulated RT.[73] Compared with adjuvant RT, neoadjuvant RT is associated with improved long-term patient survival.[90] A randomized, multicenter, controlled study conducted in patients with resectable HCC and PVTT reported that neoadjuvant 3-DCRT significantly reduced HCC-related mortality and HCC early recurrence rates compared with surgery alone.[91] Histologically, the primary tumor and PVTT show complete necrosis.[92] For HCCs with PVTT in the main trunk, the 5-year survival rate after neoadjuvant RT followed by hepatectomy is 20% higher than after hepatectomy alone (34.8% vs 13.1%).[93] For patients in the waitlist for LT, SBRT helps to downsize or stabilize tumors before LT without notable side effects.[94,95]

Recently, selective internal RT, namely, transarterial radioembolization (TARE), has shown promise for patients with HCC. TARE is a microembolic procedure that delivers radioactive particles (eg, yttrium-90 microspheres [Y-90]) to the tumor site through the tumor feeding artery. Accumulating evidence has demonstrated the safety and efficacy of Y-90 radioembolization for HCC.[96–105] A randomized, Phase 2 study of 179 patients with Barcelona Clinic Liver Cancer stage A or B demonstrated that Y-90 radioembolization led to a significantly longer time to progression (>26 months) than conventional TACE and reduced the drop-out rate from transplant waitlists.[97] Moreover, 20% of patients with locally advanced unresectable HCC with intrahepatic portal vein thrombosis were successfully downstaged to surgery after neoadjuvant TARE.[98] Patients who underwent liver surgery (LT or hepatectomy) after neoadjuvant TARE had a median OS of 47 months and a 5-year OS rate of 86%.[99] Approximately 10% of the total functional remnant liver volume increased after 40 days of neoadjuvant TARE before LR.[100–102] Hence, TARE might provide a survival benefit for patients with HCC with large tumors and major vessel invasion.[104] Finally, TARE minimizes alterations to the hepatic arterial flow and is therefore suitable for most patients with HCC with or without good liver function.[103] Few adverse events (AEs) were observed in patients with main PVTT and severe cirrhosis.[96] Despite its advantages and potential therapeutic value, TARE does not appear as beneficial as targeted drugs, such as sorafenib.[105,106] Hence, proposed prognostic stratification may help to better identify patients for whom TARE can be indicated and contraindicated.[103,107] High tumor-absorbed radiation doses and low serum alpha-fetoprotein (AFP) levels were also found to be significantly associated with successful downstaging.[98]

Neoadjuvant Ablation Therapy

Tumor ablation is a form of locoregional-directed therapy in patients with HCC. Local ablation includes percutaneous ethanol injection therapy (PEIT), microwave ablation (MWA), nanoparticle-based photothermal ablation (PTA), and RFA. In 1987, Takanashi et al demonstrated that PEIT is a valuable treatment for HCC as 30% of the patients had completely necrotic tumors, as revealed by histopathologic analysis, and no damage to the noncancerous liver parenchyma distant to the injected sites was observed.[108–110] In terms of high-risk patients with unresectable multifocal tumors, LR combined with intraoperative RFA could be safe and effective.[111] Because LR has short operative times and is associated with minimal blood loss, RFA was considered a part of a multimodal therapeutic regimen.[112–114] For LT candidates with unresectable HCC, RFA prolongs wait times for cadaveric livers,[23,115] and 56% of patients with advanced HCC are successfully downstaged to LT criteria.[116] Mazzaferro et al showed that RFA is more suitable for patients with small tumors (<3 cm), pretreatment AFP levels of >1000 ng/mL, and those who receive short-term therapy.[117,118] However, because of new metastatic diseases that develop in approximately 30% of patients after undergoing RFA, multimodality treatment approaches that include RFA should be explored.[24] At present, there are no surrogate markers to determine the optimal interval between locoregional therapies and definitive therapy (LT or LR).[119]

Similar to RFA, MWA also exerts effective antitumor effects in terms of local tumor control, treatment-related complications, and long-term survival.[120] Recently, PTA has been intensively investigated. However, PTA has certain shortcomings, such as the poor biocompatibility of most PTA agents, potential long-term toxicity, and limitations to surface tumors because of insufficient penetration depth of near-infrared light for deep abdominal tumors. Hence, a minimally invasive laparoscopic-assisted PTA method may be effective for HCC.[121] Finally, compared with RFA +

TACE, the neoadjuvant MWA + TACE strategy provides more durable disease control in patients with early-stage HCC.[122] MWA may be superior to PEIT for the local control of moderately or poorly differentiated small HCC.[123]

Neoadjuvant Systemic Therapy (NST)

NST is a broad concept and refers to a series of systemic drug delivery strategies. NST was originally developed for patients with advanced unresectable HCC as a palliative treatment and did not play a relevant role in the neoadjuvant setting. Recently, new evidence of NST for HCC has emerged, and some experts believe that a new era of the application of NST for HCC is on the horizon.[27,73,124–126] Presently, the major NSTs for patients with HCC involve tyrosine kinase inhibitor (TKI) therapy, immunotherapy, and gene/cell therapy.

Neoadjuvant TKI Strategy

Since the approval of sorafenib in 2007, TKIs have played an extremely important role in HCC treatment.[127–130] Most TKIs have multiple targets; for example, cabozantinib has nine targets (MET, VEGFR1, VEGFR2, VEGFR3, ROS1, RET, AXL, NTRK, and KIT). Thus, several signaling pathways involved in the occurrence and development of HCC could be targeted by TKIs. The safety and feasibility of TKIs as NATs for HCC were then explored.[131–137] For patients with unresectable HCC, a subset analysis of a sorafenib study database showed a difference of approximately 10 months in the OS between patients who received and did not receive sorafenib before surgical resection.[136,138] No serious adverse effect of preoperative sorafenib administration was observed during and immediately after LR.[137] For patients with locally advanced HCC who were awaiting LT, the drop-out rate of patients receiving NAT was less than that of those treated with NAT for <6 months.[131,134] Downstaging from beyond the MC using neoadjuvant sorafenib therapy was correlated with better post-LT tumor event-free survival and longer OS.[139] However, compared with TACE alone, the combination of TACE and sorafenib before LT did not result in significant benefits.[133] Thus, sorafenib administration before LT appears to be associated with an increase in acute graft rejection and biliary complications.[132,135] Other TKIs, such as lenvatinib, regorafenib, and cabozantinib, have been administrated as NATs in multiple solid tumors, such as thyroid cancer, renal cell carcinoma, and rectal cancer, and promising results were observed, but few studies have been published on TKIs as NATs for HCC.[140–144] Finally, to evaluate the survival variation of LR/LT after TKIs, a statistical model that allows personalized survival prediction using baseline clinical features is warranted.[145,146] According to the high expression level of molecular markers such as BRAF-V600E and EGFR in tumor biopsy specimens or peripheral blood, a dual-targeted therapy strategy with multiple targets is also worthy of investigation.[147–149]

Neoadjuvant Immunotherapy (NIT) Strategy

Immune escape plays an important role in HCC development. Alterations in major histocompatibility complex class I and aberrant expression of tumor neoantigens induce the activation of tumor-killing T cells.[36,150] The elimination of cancer-related immunosuppression, which is a crucial treatment strategy for HCC, is an important issue.[57,150,151] Recently, immune checkpoint inhibitors (ICIs) were found to have significant antitumor effects in HCC through targeting either programmed cell death (PD) receptor/CTLA-4 on T cells or its ligands PDL-1 and PDL-2 on tumor cells.[152–160] The current evidence for NIT in HCC is mainly focused on patients with macrovascular invasion, multifocal disease, or large tumors requiring vascular resections.[161] For unresectable HCC, lenvatinib plus pembrolizumab has shown promising antitumor activity (median OS, 22 months; objective response rate [ORR], 46%).[152,153] Dual PD-L1/VEGF blockade (atezolizumab–bevacizumab) resulted in better OS and progression-free survival outcomes than sorafenib or other targeted drugs.[157,158,160,162] More than 20% of human HCCs that do not respond to single agents could benefit from this combination.[163,164] The combination of nivolumab + ipilimumab (Check Mate 040) led to an ORR of 32% in patients who previously treated with sorafenib.[165] The toxicities were manageable, with no unexpected safety signals. In studies on NITs for unresectable HCC, the rate of successful downstaging to surgical intervention ranged from 13% to 46%, and a near-complete pathologic response was observed.[158,165–168] According to these evidences, a study named HIMALAYA was conducted to assess the efficacy and safety of durvalumab plus tremelimumab as first-line treatment in advanced HCC (NCT03298451).[169] For cancers with distant metastases, NIT has significant therapeutic efficacy compared with the use of single adjuvant immunotherapy after primary tumor resection.[170] Besides locoregional

therapies, NIT is expected to lead to HCC downstaging from unmet MC.[156] Comparable with patients who met the LT criteria, successful downstaging of HCC to within the LT criteria was associated with a low rate of HCC early recurrence and excellent post-transplant survival.[171] Despite the many benefits of NIT, no consensus has been reached on its application in a transplant setting because activated T cells may cause allograft rejection.[156,172,173] Some evidence appears to support that an optimal time interval exists between the termination of NIT and LT.[119,156,172]

Additionally, because surgical resection is associated with high early recurrence rates, the exploration of immunotherapy for resectable (early-stage) HCC may maximize patient benefits.[30,53] Several clinical studies are currently focusing on this issue.[174,175] An ongoing randomized Phase II pilot trial showed that treatment for 6 weeks with nivolumab + ipilimumab led to a pathologic complete response rate of 25% in patients with resectable HCC; the NIT regimen was safe, and surgical resection was not delayed.[155,176] The OS and 2-year recurrence rates of the study are highly anticipated. Studies on NIT are currently underway to evaluate the safety of the combination of TKIs + ICIs or dual ICI therapy before hepatic resection in patients with locally resectable HCC. Furthermore, the efficacy and the development of immune-related AEs (irAEs) appear to be impacted by the time window between NIT and surgery.[156,172] In an animal model, smaller doses of NIT scheduled close to the time of surgery may have led to optimal antitumor immunity and improved severe irAEs.[170] Two cycles of NIT appear to be a tolerable neoadjuvant dosing schedule, in which less toxicity but equal effectiveness is observed.[177] Overall, the use of NIT for the treatment of HCC in a preoperative setting is yet to be explored,[178] and thus, more randomized controlled trials (RCTs) are warranted (Table 1).

Neoadjuvant Gene/Cell Therapy Strategy

With an in-depth understanding of the biological behavior of HCC and the development of cell/genetic engineering technologies, an increasing number of potential approaches are being explored as NITs in HCC. Most of these approaches are still at preclinical or early clinical stages. The mainstay approaches involve the use of chimeric antigen receptor (CAR) T cells, allogeneic natural killer (NK) cells, and oncolytic viruses.[178–180]

Because 70% of HCCs express glypican 3 (GPC3), GPC3-targeted CAR T cells could eliminate GPC3-positive HCC cells by inducing perforin- and granzyme-mediated apoptosis or by reducing Wnt signaling in tumor cells.[181] Six registered Phase 1 studies are underway to evaluate the efficacy, tolerance, and safety of GPC3-targeted CAR T cells (NCT04121273, NCT04506983, NCT03198546, NCT02905188, NCT03884751, and NCT03980288). Other modified CAR T cell therapies are also being explored. For instance, a study of CD147-targeted CAR T cells administered by hepatic artery infusion for advanced HCC is underway (NCT03993743).[182,183] Approximately 10 registered trials have been conducted to assess the safety and efficacy of allogeneic NK cells in patients with HCC (NCT04162158, NCT02008929, NCT04011033, NCT04106167, and NCT03203005). Apart from the sequence of NK therapy to LR, NK cell treatment was found to be well tolerated and resulted in no HCC early recurrence after LT (NCT01147380).[184] NK cell-based anti-HCC therapeutic strategies alone or in combination with other therapies are highly promising for HCC treatment.[185] Finally, vaccinia virus-based oncolytic immunotherapy, which is designed to preferentially replicate in and destroy tumor cells, does not improve OS as a second-line therapy after sorafenib failure, but it may be advantageous in the treatment of patients at earlier disease stages (NCT03071094).[186] Although few trials have been conducted on neoadjuvant gene/cell therapy for HCC, theoretically, the approaches would have potential tumor-killing effects.

Combination Therapy

Although the function of NATs is increasingly obvious in HCC treatment, the rate of successful tumor downstaging or reduction of the risk of early recurrence are still not ideal. Several researchers have attempted to combine two or more treatments. NATs based on different mechanisms seem to have synergistic antitumor effects.[187,188] The combination of ICIs and TKIs has been described in the section on systemic therapy.[124] In clinical practice, complete tumor excision using unique locoregional therapy is difficult because local or remote microlesions are present in most patients with HCC.[189–191] Hence, combination therapy, such as TACE + RFA, HAIC + RFA, or TACE + RFA + ICIs, is necessary.[192] Locoregional therapy has been shown to induce a tumor immune response.[187,192–196] For instance, RFA-derived tumor antigens led to the initiation of a systemic antitumor immune response that boosted the antitumor effect of ICIs.[197]

Table 1 Clinical Trials Investigating Tyrosine Kinase Inhibitors and Immune Checkpoint Inhibitors as NATs for HCC

NO.	Identifier	Phase	BCLC Stage	Treatment Arms	Primary Endpoint(s)	Setting
1	NCT03630640	2	A or B	Nivolumab + electroporation	Local RFS	NAT/AT
2	NCT03337841	2	0 or A	Pembrolizumab + surgery/ablation	One-year RFS rate	NAT/AT
3	NCT04727307	2	0 or A	Atezolizumab + Bevacizumab + RFA	Two-year RFS rate	NAT/AT
4	NCT03510871	2	B or C	Nivolumab + ipilimumab	Tumor shrinkage	NAT
5	NCT03299946	1b	N/A	Cabozantinib + nivolumab + surgery	Safety	NAT
6	NCT03867370	Ib/II	N/A	Toripalimab (JS001)/ Toripalimab (JS001) Lenvatinib	Pathological response rate	NAT
7	NCT04850040	2	0 or A	Apatinib Mesylate+ Camrelizumab+Oxaliplatin	(MPR) 10%	NAT
8	NCT03578874	2	N/A	Sorafenib, capecitabine, oxaliplatin	Resectability	NAT
9	NCT04224480	1	B	Pembrolizumab	Recurrence rate	NAT
10	NCT04615143	2	A or B	Tislelizumab	MPR rate	NAT
11	NCT04174781	2	A or B	Sintilimab + TACE	PFS	NAT
12	NCT04850157	2	0 or A	Tislelizumab + IMRT	RFS	NAT
13	NCT04930315	2	B/C	Apatinib Mesylate + Camrelizumab	1-year recurrence-free rate	NAT/AT
14	NCT04123379	2	N/A	Nivolumab+ BMS-813160+ BMS-986253	MPR+STN	NAT
15	NCT01507064	2	N/A	Sorafenib + laser ablation	Complete tumor ablation rate	NAT
16	NCT04857684	1	A or B	SBRT + Atezolizumab + Bevacizumab	Proportion of Ade	NAT
17	NCT04888546	Ib/II	A or B	Anlotinib hydrochloride capsules + TQB2450 injection	pCR rate	NAT
18	NCT04425226	N/A	N/A	Pembrolizumab Injection+ Lenvatinib Oral Product	RFS	NAT
19	NCT04658147	1	N/A	Nivolumab + Relatlimab	Surgery Numbe	NAT
20	NCT04954339	2	B/C	Aatezolizumab plus Bevacizumab	pCR	NAT
21	NCT04954339	2	B/C	Aatezolizumab plus Bevacizumab	pCR	NAT
22	NCT04653389	2	B/C	Sintilimab Injection + TACE + Radiotherapy	EFS	NAT
23	NCT03097848	N/A	B/C	RFA + Sorafenib	1-year DFS	NAT
24	NCT01337492	1	A or B	Nexavar	Adverse events	NAT
25	NCT04521153	N/A	B/C	Camrelizumab+Apatinib Mesylate+ TACE + radical surgery	3-year EFS	NAT
26	NCT01182272	2	A or B	Sorafenib tosylate	Antiangiogenic effects	NAT
27	NCT04443322	N/A	A or B	Durvalumab + Lenvatinib	PFS + RFS	NAT

Abbreviations: RFS, recurrence free survival; RFA, radiofrequency ablation; NAT, neoadjuvant therapy; AT, adjuvant therapy; SBRT, stereotactic body radiation therapy; IMRT, intensity modulated radiation therapy; MPR, major pathological response; HAIC, hepatic artery infusion chemotherapy; STN, significant tumor necrosis; pCR, pathological complete response; PFS, progression-free survival; OS, overall survival; EFS, event free survival; TACE, transartery chemoembolization.

Tremelimumab (a CTLA-4 monoclonal antibody) in combination with tumor ablation led to the accumulation of intratumoral CD8+ T cells and resulted in a 6-month progression-free survival rate of 57.1% in patients with refractory HCC.[198] Patients with recurrent HCC could achieve a longer survival time following combined treatment. TACE + sequential RFA within 30 days is more effective for recurrent HCCs. A certain time interval is required for the treatment of large or multiple HCCs but may not be necessary for the treatment of solitary medium-sized HCCs.[199,200] Some trials of TACE + ICIs and/or TKIs are currently underway. Some examples are as follows: cabozantinib + ipilimumab/nivolumab and TACE in patients with HCC (NCT04472767), TACE + SBRT followed by dual immunotherapy for downstaging HCC (NCT04988945 and NCT03817736). For patients with potentially resectable HCC, TACE + HAIC vs HAIC, TACE + sintilimab injection, and TACE + durvalumab + bevacizumab therapy are being explored as preoperative strategies (NCT03591705, NCT04174781, and NCT03778957). However, not all combination therapies can reduce the tumor burden or improve prognosis; for example, HAIC + cisplatin before RFA did not significantly decrease the early recurrence rate in patients with early-stage HCC;[192] hence, treatment decisions should be made strictly on the basis of clinical evidence-based results.

Selection of Appropriate NATs

As results about NATs applying in patients with HCC are not so strong at the moment, the identification of patients who will benefit and the selection of the appropriate NAT in advance are challenging.[27] Previous models that were developed to predict the treatment effect and prognosis of patients are relatively imprecise and are mainly focused on the tumor burden, lesion number, tumor vascularity pattern, histological grade, hepatic reserve, and performance status.[201,202] Multidimensional and multilevel evaluations are needed to predict the effect of NATs (eg, the combination of molecular/cell biology and imaging).

With a more in-depth understanding of the molecular biological behavior of HCC, numerous biomarkers have been established to predict the effect of NATs. In liquid biopsy, the serum AFP level was found to be correlated with tumor early recurrence after LT, and patients with AFP levels of >400 ng/mL responded well to ramucirumab (a VEGF-2 inhibitor).[201,203–205] The reinvigoration of circulating exhausted-phenotype CD8+ T cells induces a strong immunological response to pembrolizumab.[206] Lenvatinib-treated responders showed greater increases in FGF19 and FGF23 levels than nonresponders, but higher baseline VEGF, ANG2, and FGF21 levels were correlated with shorter OS after lenvatinib or sorafenib treatment.[207] Circulating tumor cells, which escape from the tumor site, are the primary source of metastases or post-LT recurrence and have been shown to predict HCC early recurrence after LR and LT.[208,209] Moreover, the integration of transcriptomic and genomic data provides a global tumor picture and describes the escape mechanisms.[210] Analysis of circulating tumor DNA carrying a cancer-specific tumor framework, mutational load, immune composition, and antitumor immunity as well as immunosuppressive genetic and epigenetic aberrations enables monitoring of the effect of NAT in HCC in a noninvasive, dynamic manner.[211] The expression levels of *TP53, RET, FGFR3*, and *APC* in the plasma were significantly higher in patients with multiple tumors or with metastasis than in patients with single tumors, which indicates that patients with high mutant allele frequency in these genes are more suitable for NAT.[212] The predictive role of other biomarkers, such as des-γ-carboxy prothrombin, lens culinaris agglutinin-reactive AFP, and proteins induced by vitamin K absence/antagonist-II, are being explored.

In traumatic biopsy, the expression of PD-1 on subdominant T (CD8+) cells was found to be correlated with a favorable response to PD-1/PD-L1 blocking antibodies by enhancing CD8+ T cell survival and not by enhancing their proliferation.[35,37,213] The low expression of Batf3 (+) DC in pretreatment tumor biopsies is related to relapse after neoadjuvant ipilimumab + nivolumab.[214] Pre-existing T cell infiltration and/or PD-L1 expression in tumors may serve as indicators of the clinical response.[206] The expansion and activation of CD103 (+) DC progenitors at the tumor site enhances tumor responses to therapeutic PD-L1.[215] Increased IL-6 expression in pre-RT serum and tumor tissues was significantly associated with resistance to RT.[91] Additionally, compared with the intermediate VEGF/FGF group, the VEGF/FGF-enriched groups demonstrated improved OS with lenvatinib administration.[207] Recent studies found that lenvatinib reduced the tumor PD-L1 level and Treg differentiation to improve anti-PD-1 efficacy by blocking FGFR4. Furthermore, the levels of FGFR4 expression and Treg infiltration in the tumor could serve as biomarkers for screening patients with HCC for lenvatinib + anti-PD-1 combination therapy.[163,216] For patients resistant to NAT within the

treatment window, combinations of novel signal pathway inhibitors may revive the effect of TKIs or immunotherapy.[147] Other biomarkers, such as TMB, MSI/DMMR, EBV infection, and *POLE*/*ALK* gene expression, also play an important role in predicting the effects of NAT.[147,217–219]

Overall, patients with a high tumor burden, high risk of recurrence, and potential resectable tumors are suitable for undergoing NAT. Although many biomarkers have been found to be associated with the effect of NAT, few have been confirmed by large RCTs. Thus, the comprehensive evaluation of these predictors is requisite in clinical practice.

Conclusion

A novel era for HCC treatment is imminent. NAT is the bridge leading to the development of personalized therapies and is constantly improving under the existing framework. In terms of treatment optimization, researchers should consider local and global aspects, short- and long-term effects, and toxicity. The main obstacle to adequate patients' selection derives from the absence of predictive biomarkers. Future studies of NAT should focus on the identification of biomarkers of treatment response, explore the mechanisms of resistance, and standardize endpoints of NAT. Large RCTs are required to ensure the optimal components and sequence of multimodality therapy.

Abbreviations

HCC, hepatocellular carcinoma; NAT, neoadjuvant therapy; NAC, neoadjuvant chemotherapy; LT, liver transplantation; OS, overall survival; VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; LR, liver resection; HAIC, hepatic arterial infusion chemotherapy; PVTT, portal vein tumor thrombosis; CCRT, concurrent chemoradiotherapy; SBRT, stereotactic body radiotherapy; TARE, transarterial radioembolization; AFP, alpha-fetoprotein; PEIT, percutaneous ethanol injection therapy; MWA, microwave ablation; PTA, photothermal ablation; NST, neoadjuvant systemic therapy; TKI, tyrosine kinase inhibitor; NIT, neoadjuvant immunotherapy; ICIs, immune checkpoint inhibitors; RCTs, randomized controlled trials.

Consent for Publication

All authors have agreed on the contents and publication of the manuscript.

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All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared that they have no conflicts of interest to this work.

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