Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/16/20240596

Immunotherapy of hepatocellular carcinoma: Current status

Xinyu Zhao

Key Laboratory of Cell Differentiation and Apoptosis of Ministry of Education of China, Department of Pathophysiology, Shanghai Jiao Tong University School of Medicine, Shanghai, China

1911441109@mail.sit.edu.cn

Abstract. Hepatocellular carcinoma (HCC), the predominant leading hepatic malignancy, is marked by an unfavorable prognosis. Traditional therapeutic modalities such as surgery, chemotherapy, and radiofrequency ablation offer efficacy to a constrained subset of HCC patients at an early stage. Until a brief time ago, tyrosine kinase inhibitors (TKIs) such as Sorafenib and Lenvatinib have been reported to be the sole authorized systemic therapies for individuals with advanced HCC. However, these treatments yielded only modest improvements in survival and were associated with a plethora of potential adverse effects. The confluence of rapid advancements in genetic engineering and synthetic biology has fostered the emergence of an array of innovative immunotherapeutic interventions to address advanced HCC. These interventions encompass immune checkpoint inhibitors, CAR-T cell therapy, engineered cytokines, therapeutic cancer vaccines, bispecific antibodies (BsAbs) therapy and so forth. The majority of immunotherapeutic approaches have currently yielded certain therapeutic effects in experimental and preclinical investigations, with a small fraction having transitioned to clinical application. Within this comprehensive assessment, the prevailing landscape and forward momentum about distinct immunotherapeutic strategies within the HCC treatment milieu are introduced. The focus will be placed on benefits and limitations, as well as current research on immunotherapies and developing information on HCC treatment.

Keywords: Immunotherapy, Immune Checkpoint Inhibitors, CAR-T Cell Therapy, Bispecific Antibody, Hepatocellular Carcinoma.

1. Introduction

Liver cancer stands as the sixth most common primary cancer in humans., boasting the unfortunate distinction of being one of the most widespread malignancies globally. With a fourth-place ranking in terms of lethality worldwide, liver cancer is projected to afflict over a million individuals annually by the year 2025. Among these cases, hepatocellular carcinoma (HCC) makes up approximately 80-90% of primary liver cancer cases., characterized by a grim outlook and a modest 18% survival rate over five years.[1], thereby imposing substantial burdens on healthcare systems. Predominantly afflicting males aged 60 to 70, HCC risk factors encompass a familial background of liver cancer, hepatitis B and C virus infections (HBV and HCV), heavy alcohol consumption and nonalcoholic steatohepatitis (NAFLD). While anti-HBV and anti-HCV therapies offer some risk reduction, they fall short of complete prevention. Serum alpha-fetoprotein (AFP) serves as a widely employed as well as pivotal diagnostic marker for early HCC detection and treatment monitoring. Nevertheless, HCC often eludes

DOI: 10.54254/2753-8818/16/20240596

detection until it reaches intermediate to advanced stages [2]. Consequently, the survival rate after advanced HCC liver resection remains disappointingly low, as evidenced by extensive data.

Advanced HCC treatment options have significantly progressed with the integration of radiation embolization, percutaneous ablation, liver transplantation and transarterial chemoembolization (TACE). However, the selection of these therapies hinges predominantly on factors such as tumor burden, location, and accompanying medical conditions [3]. For more than a decade, the most crucial pillars in treating advanced HCC are systemic molecular therapies. These therapies encompass first-line medications such as the orally administered multi tyrosine kinase inhibitors (TKIs) sorafenib, as well as alternative choices in the second-line like regorafenib and lapatinib. A potent immune response has the capacity to either eliminate cancerous cells or weaken characteristics and functions. Nevertheless, tumor cells have developed tactics or mechanisms, including compromised express of antigen and attracting immune-inhibiting cell groups, in order to elude immune monitoring, thereby hampering immune response against cancer cells.

In the past few years, immunotherapy has been highlighted as a promising avenue for the management of cancer. This approach includes CAR-T cell therapy, bispecific antibodies (BsAbs) therapy, cytokines, cancer vaccines and immune checkpoint inhibitors (ICIs). Immunotherapy has demonstrated remarkable efficacy in other solid tumors, ushering in a transformative era in the management of HCC. Therefore, by elucidating the underlying principles of immunotherapy and advancements in therapy in the context of HCC treatment, the challenges and benefits for effectively addressing HCC patients are underscored.

2. Immune checkpoint inhibitors (ICIs)

Immune checkpoints are composed of regulatory receptors that either inhibit or enhance the immune system's activity. Tumor cells employ strategies such as reducing the presence of surface proteins that trigger immune activation or increasing the production of proteins binding to immune-inhibitory receptors. These tactics establish an environment conducive to immune tolerance, shielding tumor cells from immune attack. ICIs represent a category of monoclonal antibodies and are designed to disrupt these interactions between tumors and immune cells by impeding the engagement between immune regulatory molecules and their corresponding ligands, thus enhancing the ability of the immune system to combat tumors [4]. Currently, ICIs are under investigation both as standalone treatments and combination with other systemic treatments for managing HCC. Those targeting receptors like PD-1, PDL1, CTLA-4, TIM-3, and so forth, have displayed remarkable degrees of safety and effectiveness in the management of HCC.

Compared to other conventional therapies, ICIs have some advantages in treating solid tumors including HCC. Firstly, ICIs unleash the immune system's ability to identify and assail cancerous cells more effectively. They interrupt the suppressive cues that cancer cells employ to elude immune recognition, thus promoting a stronger immune response against HCC. Besides, long-lasting effects and lower toxicity were reported in many researches. ICIs tend to have a more favorable side effect profile compared to traditional chemotherapies, which makes them a more tolerable option for many patients. Some patients experience durable responses to ICIs, meaning that the benefits of treatment can extend over a more extended period compared to traditional therapies. Furthermore, ICIs are able to be customized for individual patients according to their specific immune profiles, potentially increasing their effectiveness. Nowadays, clinical trials and real-world data have shown promising results with ICIs, both in combination with different therapies and as monotherapy. They have the potential to enhance survival outcomes and the quality of life in patients with HCC.

Nivolumab, a PD1 inhibitor, obtained accelerated sanction in America for second-line intervention among patients who got advanced HCC post-sorafenib treatment. Due to the ability of acting upon PD-1 and PD-L1, Pembrolizumab and atezolizumab have been progressively assimilated into treatment protocols or recommendations across numerous nations, constituting recommended therapeutic options for HCC patients. The administration of pembrolizumab and nivolumab yields clinical remission rates of 15 to 20%, encompassing total recoveries in the range of 1 to 5%. These remissions exhibit resilience

DOI: 10.54254/2753-8818/16/20240596

and correlation with protracted survival durations. Noteworthy findings from the CheckMate 040 trial indicated an average response lasting for 17 months with nivolumab in 48 participants within the escalating dosage segment, culminating in two-year survival percentage exceeding 80% [5]. Besides, a pivotal phase III clinical inquiry called KEYNOTE-240, subjected 413 patients to pembrolizumab following sorafenib intervention and juxtaposed their outcomes against a placebo cohort. The investigation yielded statistically elongated survival (HR 0.78; P=0.023). This result corroborated sustained benefits from pembrolizumab for an extended period. Notably, roughly 20% of individuals subjected to pembrolizumab sustained non-progression status beyond 1 year, in contrast to the sub-7% incidence within the reference group. Furthermore, a comparison between nivolumab and sorafenib was effectuated in a phase III CheckMate 459 trial, which encompassed 743 patients naïve to systemic interventions. The study underscored the protracted survival of nivolumab recipients relative to those administered sorafenib, with average survival spans of 16.4 versus 14.7 months (HR 0.85; P=0.07) [6]. Tislelizumab, a humanized monoclonal antibody with heightened PD-1 affinity, exhibited commendable tolerability and effectiveness in HCC patients. A randomized phase 3 trial (NCT03412773) is presently underway, juxtaposing sorafenib and tislelizumab as first-line modalities for unresectable HCC adults, thereby poised to furnish deeper insights into the therapeutic potential of these interventions.

Tremelimumab, functioning as a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, showcased its partial response potential in a phase 2 trial involving a cohort of 20 patients, registering in 17.6% of patients with HCC. It merits acknowledgment that these instances of partial response endured for durations of merely 3.6, 9.2, and 15.8 months [7]. Notwithstanding the reasonable safety profile exhibited by tremelimumab in this study, the objective response rate proved to be modest. This outcome prompted conjecture that synergistic combination regimens could potentially augment therapeutic efficacy. In addition, LAG-3 and TIM-3 represent additional candidates capable of modulating and inciting anti-tumor immune reactions. Liu and colleagues conducted a study examining the presence, role, and control of pathway involving Tim-3 and galectin-9 within individuals afflicted by HBV-associated HCC. Their investigation revealed that the interplay between Tim-3 and galectin-9 detrimentally affected the functional capacity of T cells in HCC, with Tim-3 expression exhibiting a negative correlation with the clinical prognosis of HBV-related HCC patients. LAG3 exhibits a strong binding affinity for MHC class II molecules, and its expression is heightened following T cell stimulation, culminating in a suppressive regulatory signaling for T cells. Guo and collaborators observed a notable elevation in serum LAG-3 levels in individuals suffering from HCC as opposed to healthy subjects [8]. Furthermore, people expressing high LAG-3 concentrations experienced a less favorable forecast following TACE. Those preliminary investigations underscore the capacity for combining LAG-3 and TIM-3 as well as provide backing for the following implementation of combination treatment involving various immune checkpoint inhibitors.

Ongoing clinical trial outcomes manifest that patients subjected to monotherapy utilizing ICIs exhibit a diminished response rate. Hence, the amalgamated utilization of ICIs in conjunction with adjunctive interventions stands as the impending trajectory. In 2020, a globally encompassing randomized phase 3 study, IMbrave150, furnished compelling evidence of the efficacy of atezolizumab synergized with the anti-angiogenic agent bevacizumab. This combinatorial approach imparted a marked diminution in the hazard of mortality among individuals grappling with advanced unresectable HCC, alongside pronounced enhancements in the caliber of survival. Concurrently, this fusion of pembrolizumab with lenvatinib, a potent TKI, engendered a noteworthy overall response rate (ORR) which resulted in 46%. Within the cohort of participants afflicted by unresectable HCC, comprehensive response (CR) and partial response (PR) were ascertained in 11% and 35% of cases, respectively [9]. This synergy between pembrolizumab and lenvatinib underscores a promising therapeutic avenue, fostering a substantial clinical response (CR and PR) encompassing a significant portion of the patient populace. In preclinical and clinical settings, some recent investigations have illustrated that the concurrent utilization of ICIs in conjunction with TACE, radiofrequency ablation (RFA), and radiotherapy holds the potential to enhance the effectiveness of immunotherapeutic interventions against tumors. Furthermore, a phase Ib/II clinical study is presently in progress to assess the utility of ocrelizumab combined with the chemotherapy

DOI: 10.54254/2753-8818/16/20240596

regimen FOLFOX4 as a critical therapeutic choice for patients with advanced HCC. A comprehensive overview of clinical trials conducted over the past three years about the application of ICIs in HCC therapy is also available.

Although ICIs have propelled the domain of HCC therapy forward, a significant portion of patients, regrettably, exhibit no response to this and some individuals may paradoxically worsen and develop a condition of hyper-progressive disease. One of the foremost limitations of ICIs in HCC treatment is the heterogeneous nature of the disease. HCC arises from diverse underlying causes, including NAFLD, HBV and HBC infections, and excessive alcohol consumption. Consequently, not all HCC patients respond equally to ICIs. Additionally, while ICIs generally have a more favorable side effect profile compared to traditional chemotherapy, immune-related adverse events (irAEs) could be induced. Moreover, whereas a few HCC patients initially respond favorably to ICIs, resistance can develop over time, limiting the effectiveness of these drugs. There is a scarcity of data concerning the mechanisms accountable for HCC's resistance to immunotherapy.

3. CAR-T cell therapy

Chimeric antigen receptor T-cell (CAR-T cell) therapy has been considered as an pioneering modality wherein T cells are procured from the patient, subsequently undergoing genetic engineering to acquire the capacity to selectively recognize and bind to cancer-associated antigens. Following reintroduction into patients, those engineered CAR-T cells undertake the task of homing in on tumor antigens, thereby triggering their activation and executing cytotoxic functions. The pivotal rationale underlying this approach is the precise targeting of tumor-specific antigens that are characterized by minimal expression in healthy tissues, thereby conferring an optimal therapeutic effect while mitigating the occurrence of adverse effects.

The principal benefit of CAR-T cells, which are lymphocytes that have undergone genetic modification, lies in their capacity to identify extracellular antigens independently of HLA molecules, thereby obviating the necessity for antigen presentation via MHC molecules on the cell surface [10]. This feature renders a larger cohort of cancer cells susceptible to immune attack. Furthermore, it can target tumor cells precisely and be personalized for every patient, providing a novel and promising avenue for patients who have exhausted other treatment options. Consequently, the utilization of CAR-T cell therapy in HCC has garnered significant scrutiny and interest in recent times. A plethora of potential targets has undergone scrutiny within the HCC landscape, encompassing antigens such as MUC1, AFP, MAGE, GPC-3, EpCAM, NY-ESO-1, hTERT, CD133, NKG2DL, CD147 and so on.

GPC-3 is a proteoglycan that exhibits overexpression in HCC and the Wnt signaling pathway is activated by it, thereby promoting HCC development. A trial involving 13 patients assessed the efficacy of CAR-T cells targeting GPC-3. The trial's findings displayed the security of this treatment, with clear and positive responses noted in two patients. Various ongoing experiments are actively investigating the potential of GPC-3-targeted CAR-T cells.

Furthermore, targeting CD133 has shown promise during clinical investigations. Repeated infusions of these cells were associated with extended periods of disease stability in a phase 1 research involving 23 patients who had advanced HCC and tumors expressing CD133. Remarkably, 14 patients experienced disease stability and 3 patients achieved remission. Subsequently, CAR-T cells aiming CD133 exhibited a disease control rate of 43% over 6 monthstudy in a clinical study involving 21 patients [11]. Ongoing clinical trials include investigations into EpCAM-targeted CAR-T cells (NCT02729493). In addition, other researches about MUC1-targeted CAR-T cells (NCT02587689) are also in progress. Nowadays, many experiments are dedicated to the development of CAR-T cells engineered to target multiple antigens, to enhance their therapeutic efficacy.

AFP exhibits high fetal expression but minimal presence in adults; however, its re-expression becomes evident in the context of adult-onset HCC. Distinct CAR-T cells were devised by Liu et al., and these cells are able to selectively engage the AFP158-166 peptide-MHC complex, thereby enabling the lysis of HLA-A*02:01+/AFP+ tumor cells. To validate the strategy, the security and effectiveness of these CAR-T cells in HCC patients whose tumors express AFP were successfully assessed in a phase

DOI: 10.54254/2753-8818/16/20240596

I clinical trial (NCT03349255) [12]. Besides, c-Met serves as an inducer of hepatocyte growth, viability, and recovery. Elevation in its expression triggers the progression of HCC and emerges as a plausible therapeutic target for HCC intervention. CAR-T cells engineered by Jiang et al. which jointly targeted PD-L1 and c-Met revealed that PD-L1+ c-Met+ HCC cells were substantially tackled by this dual-targeted approach.

CAR-T cell therapy manifested effective treatment in many experiments over the past years, but there are some limitations we need to notice. Limited target antigens in HCC can be challenging because of heterogeneity. In addition, although CAR-T cells are engineered to focus on particular antigens, there is a risk of off-target effects, where they may also attack healthy tissues expressing the same or similar antigens. This can lead to unintended side effects. Neurotoxicity and cytokine release syndrome (CRS) have been recorded in the past, which might cause worse treatment. Biomarkers for patient selection and high cost should also be taken into consideration.

4. Bispecific antibody therapy

Bispecific antibodies (BsAbs) are different with monoclonal antibodies and are predominantly generated through recombinant DNA techniques, enabling them to simultaneously bind two distinct antigens or epitopes with specificity. This dual-binding specificity allows for highly targeted and precise therapy, reducing off-target effects and potentially increasing the therapeutic window [13]. Therefore, BsAbs exhibit the capacity to potentiate immune cell activity against cancers directly and are able to target tumor-associated antigens (TAAs) as well as immune checkpoints to counteract immunosuppressive conditions within the tumor microenvironment. Consequently, in comparison to monoclonal antibodies, they offer superior advantages in the context of synergistic outcomes. Additionally, this method also mediates a diverse array of particular biological reactions. Typically, BsAbs orchestrate the recruitment and activation of immune cells to induce cancer cells destruction by facilitating the connection or interaction between cancer and immune cells.

Recently, a humanized bispecific antibody was developed, based on IgG4 and engineered to silence FcγR activity. This innovative antibody exhibited single binding affinities for both GPC3 and CD3 as well as was effectively evaluated in murine models to mitigate the risk of cytokine release. Besides, the security and effectiveness of this antibody was assessed in a phase I clinical trial, which is registered under the identifier NCT02748837. Solitomab, also known as AMG110 or MT110, is classified as a bispecific T-cell engager (BiTE) and is regarded as a humanized bispecific antibody that targets both CD3 and EpCAM. When this BiTE is administered alongside γδ T cells, it results in the near-total dissolution of hepatoblastoma cell lines and HCC in vitro experiments [14]. Beyond its application in liver cancers, bispecific antibodies targeting EpCAM have undergone testing for their therapeutic potential against various other tumor types.

When it comes to viral antigen BsAb, a bispecific antibody was engineered to recruit T cells to the locale of HCC expressing HBx. This BsAb, created through hybrid-hybridoma technology, involves the fusion of hybridoma cell lines producing anti-HBx and anti-CD3 antibodies. When co-administered with effector cells cultivated in vitro, this antibody triggered curtailed the growth of HCC xenografts as well as apoptosis in immunocompromised mice.

Although bispecific antibodies have many benefits, there are still some limitations we need to pay attention to. BsAbs often have a shorter half-life in the body compared to traditional monoclonal antibodies. In addition, target antigen selection and off-target effects are also challenges we will face due to significant heterogeneity. Moreover, BsAbs, particularly those derived from non-human sources, can trigger an immune response in patients. This immunogenicity can lead to the rapid clearance of BsAbs from the bloodstream, reducing their efficacy.

5. Cytokines

Cytokines constitute a class of petite protein molecules with an extensive array of biological functions. These molecules are generated and secreted by immune and certain non-immune cells as a response to external stimuli. Cytokines play a pivotal role in mediating intercellular communication and exhibit a

DOI: 10.54254/2753-8818/16/20240596

wide spectrum of roles, including the control of both natural and acquired immune reactions, cellular proliferation, and the facilitation of tissue repair in cases of injury. The landscape of tumor immunotherapy has advanced significantly, ushering in a new era for cytokine-based treatments. Cytokines like interferon (IFN) and interleukin (IL) have become integral components of tumor immunotherapy. Given the limited immune cell presence in HCC, leveraging cytokines to stimulate immune cell proliferation and stimulating the attraction of immune cells represent a viable strategy to enhance the immune response against the tumor.

A meta-analysis scrutinizing IFN-α's impact revealed its potential to curtail mortality rates and premature relapse occurrences in HCC after therapeutic procedures aimed at a cure, albeit manifesting no discernible influence on late recurrence incidents [15]. In HBV-HCC and HCV-HCC cases, the divergent effects of adjuvant IFN-α on postoperative recurrence were observed, suggesting distinct tactics tailored to adjuvant IFN-α treatment contingent upon the underlying HCC background. The efficacy of adjuvant pegylated interferon (Peg-IFN) therapy was assessed in a separate meta-analysis, concerning the post-treatment survival of patients with hepatitis-related HCC after curative procedures. The findings underscored that the recurrence-free survival (RFS) and OS among patients who had undergone curative interventions could be enhanced, lacking precipitating serious adverse effects.

While IFN-α is slowly relinquishing its status as the foremost frontline anti-neoplastic therapy, the advent of long-acting Peg-IFN endures to bestow significance as an adjunctive therapeutic in HCC management. Preclinical investigations utilizing the patient-derived xenograft (PDX) HCC model have illuminated the multifaceted impact of interferon-beta (IFN-β). Beyond its antiviral role, IFN-β has demonstrated anti-cancer efficacy via modulating the p53 or JAK-STAT signaling cascades [16]. Concurrently, IL-2 engenders pleiotropic effects on the immune system, augmenting T cell proliferation and activating their anti-tumor capacities. Treatment with IL-2 among inoperable HCC patients yielded increased survival rates.

Nonetheless, cytokines administered as monotherapy have fallen short of their initial promise due to several challenges. Parenteral cytokine administration typically fails to attain therapeutic concentrations within tumors, often provoking immune regulatory points at either the humoral or cellular levelst and inducing serious toxicity. in order to surmount such barriers, cytokines are presently subject to clinical scrutiny in tandem with innovative strategies such as cancer-targeted monoclonal antibodies, newly engineered cytokine mutants (superkines), anti-cancer vaccines and chimeric antibody-cytokine fusion constructs (immunokines). These endeavors aim to safeguard cellular reactions or amplify their antibody-dependent cellular cytotoxicity (ADCC) as well as anti-cancer effectiveness within a cancer-specific context.

6. Tumor vaccines

Vaccine therapy represents a prospective strategy for harnessing the diversity observed in HCC and the complex tumor microenvironment. This method function by provoking a T cell-mediated reaction through the introduction of antigens or dendritic cells (DCs) loaded with epitopes. These strategies can be directed toward well-established HCC-associated peptides (MAGE-1, AFP, hTERT, GPC-3, SSX-2 and NY-ESO-1). Alternatively, they are able to be individualized for each patient through focusing on novel antigens specific to their tumor. Contemporary therapeutic vaccine strategies employed for HCC predominantly encompass peptides, DCs, and oncolytic viruses.

By utilizing dendritic cells loaded with antigens like MAGE-1 and AFP, a notable outcome was achieved n a phase 1/2 clinical study. This approach led to maintain the condition of the disease in 61% of patients, in contrast to those with placebo. Considering another separate phase 1/2 trial where 22 patients with early to mid-stage HCC who have matching HLA haplotypes participated, the security and effectiveness of the HepaVac-101 vaccine were assessed. A satisfactory safety profile was exhibited and an immune reaction aimed at HLA class I and II tumor peptides was observed in 37% and 53% of patients in this vaccine [17]. Currently, clinical studies are underway to evaluate vaccine therapy, either as a standalone treatment or in combination with ICIs. However, most of these trials remain unpublished or have produced unfavorable clinical outcomes.

DOI: 10.54254/2753-8818/16/20240596

7. Conclusion

Immunotherapy is expected to undergo a remarkable transformation in redefining the management of malignancies, poised to emerge as the dominant paradigm in tumor treatment due to its unparalleled specificity and heightened efficacy. Although substantial advancements have been made in current immunotherapeutic approaches for HCC, certain difficulties endure. Antibody therapies are highly specific and enable the immune system to identify and combat tumor cells with greater efficiency. However, limited applicability, drug resistance and potential side effects still need to be addressed. Additionally, immunotherapy based on cellular approaches, like CAR-T cell therapy, can be customized for patients, target specific antigens and trigger a potent and sustained immune response. Conversely, cytokine release syndrome and neurological toxicity, limited antigen selection, high cost as well and off-tumor toxicity remain major challenges that need to be overcome. Whereas tumor vaccines can target specific tumor-associated antigens, induce immunological memory and prevent certain cancers, immune evasion, insufficient antigen choices and adverse effects require further investigations. Because the efficacy of immunotherapy alone has its limitations in clinical trials, further improvement and exploring alternative solutions is what should be focused on upcoming research. Recently, combination with other therapies, including various immunotherapies and conventional therapies, often yields superior therapeutic outcomes and promotes an objective response rate than independent use. In the future, the resolution would lie in orchestrating the development of these therapies synergistically, with the aspiration of creating a significant breakthrough. Henceforth, a holistic examination to devise tailored immunotherapy treatments for patients with HCC, meticulously assessing as well as prognosticating the effectiveness of immunotherapy, and embracing treatment approaches that involve a combination of methods represent pressing inquiries needed to be addressed. These queries signify the forthcoming trajectory of investigation in the field of HCC immunotherapy as well.

References

[1] Aderhold J, Davydov V Yu, Fedler F, Klausing H, Mistele D, Rotter T, Semchinova O, Stemmer J and Graul J 2001 J. Cryst. Growth 222 701
[2] Siegel R L, Miller K D, Fuchs H E and Jemal A 2022 CA Cancer J Clin. 72 7–33
[3] Zhang B H, Yang B H and Tang Z Y. 2004 J Cancer Res Clin Oncol. 130 417-22
[4] Galle P R, Forner A, Llovet J M, Mazzaferro V, Piscaglia F, Raoul J L, Schirmacher P and Vilgrain V 2018 J Hepatol. 69 182-236
[5] Bagchi S, Yuan R and Engleman E G 2021 Annu Rev Pathol. 16 223-49
[6] Sangro B, Yau T, El-Khoueiry A B, Kudo M, Shen Y, Tschaika M, Roy A, Feng Y, Gao L and Aras U 2023 Clin Transl Sci. 16 1445-57
[7] Yau T, et al. 2022 Lancet Oncol. 23 77-90
[8] Sangro B, et al. 2013 J Hepatol. 59 81-8
[9] Guo M, Qi F, Rao Q, Sun J, Du X, Qi Z, Yang B and Xia J 2021 Front Immunol. 12 754961
[10] Finn R S, et al. 2020 J Clin Oncol. 38 2960-70
[11] Larson R C and Maus M V 2021 Nat Rev Cancer. 21 145-61
[12] Wang Y, et al. 2018 Oncoimmunology. 7 e1440169
[13] Liu H, et al. 2017 Clin Cancer Res. 23 478-88
[14] Thakur A, Huang M and Lum L G 2018 Blood Rev. 32 339-47
[15] Hoh A, Dewerth A, Vogt F, Wenz J, Baeuerle P A, Warmann S W, Fuchs J, Armeanu-Ebinger S 2013 Liver Int. 33 127-36
[16] Zhang W, Song T Q, Zhang T, Wu Q, Kong D L, Li Q and Sun H C 2014 Mol Clin Oncol. 2 1125-34
[17] Sakisaka M, Haruta M, Komohara Y, Umemoto S, Matsumura K, Ikeda T, Takeya M, Inomata Y, Nishimura Y and Senju S 2017 J Hepatobiliary Pancreat Sci. 24 109-19
[18] Löffler M W, et al. 2022 Clin Cancer Res. 28 2555-66