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Interventional therapy combined with immune checkpoint inhibitors: Emerging opportunities for cancer treatment in the era of immunotherapy

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ABSTRACT

Immune checkpoint inhibitors-based immunotherapy offers a new effective modality in the treatment of advanced malignancies. Considering the remarkable efficacy of immune checkpoint inhibitors in clinical trials, the FDA has approved a variety of immune checkpoint inhibitors for the treatment of advanced tumors. However, only limited patients with certain cancers can benefit from monotherapy of immune checkpoint inhibitors. Interventional therapy for cancer can not only destroy the primary tumors, but also regulate the immune system through different mechanisms, which provides a potential possibility for the combination of immune checkpoint inhibitors and interventional modalities in cancer treatment. This article reviews the possible synergistic mechanisms of interventional therapy combined with immune checkpoint inhibitors and summarizes the research progress of the combined therapy in cancer treatment.

Introduction

Immunotherapy, which is another important treatment modality except for surgery, radiotherapy and chemotherapy, plays an important role in the treatment of malignant tumors. In recent years, the rapid development of immunotherapy has broken the monopoly of conventional cancer treatment, especially the emergence of immune checkpoint inhibitors marks an important milestone in cancer immunotherapy. Preclinical studies and clinical trials have demonstrated that immune checkpoint-targeted agents have a promising clinical application. The US Food and Drug Administration (FDA) has approved a variety of immune checkpoint inhibitors for the treatment of melanoma, kidney cancer, non-small cell lung cancer and other malignancies. However, monotherapy of immune checkpoint inhibitors can only benefit some patients. The researchers tried to strengthen the antitumor effect through the combination of immune checkpoint inhibitors with different mechanisms of action. Results from clinical trials showed that the use of agents targeted programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) can significantly increase the objective response rate of patients with malignant melanoma and extend the survival, but at the same time, combined therapy significantly increased the incidence of immune-related severe adverse events [1–4]. Therefore, it is necessary to adopt a comprehensive treatment strategy based on immune checkpoint inhibitors, which can not only increase the objective response rate, but also reduce the treatment-related side effects [5].

With the rapid development of interventional radiology, interventional therapy has become one of the important modalities for cancer treatment, and interventional oncology has gradually developed into a new discipline. Interventional oncology is a subspecialty field of interventional radiology which aims at treating cancer or palliating the cancer-related symptoms by means of imaged-guided techniques [6]. There are varieties of techniques for interventional treatment of tumors with extensive clinical application, including intra-arterial therapies (conventional transcatheter arterial chemoembolization, drug-eluting bead transcatheter arterial chemoembolization, and radioembolization), ablation (radiofrequency ablation, cryoablation, microwave ablation, and irreversible electroporation), and brachytherapy (Iodine-125 seed, Yttrium-90 microsphere). The efficacy of interventional treatment for different tumors also varied. The study found that local-regional interventional treatment for cancer could elicit systemic immune response, but this effect was too weak to prevent local recurrence and distant metastasis effectively [7]. Because interventional treatment for cancer can regulate the immune system through different

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mechanisms, it may synergize with the immune checkpoint inhibitors to enhance the anti-tumor immune response, which provides new possibilities for cancer treatment. This article reviews the synergistic mechanisms of interventional therapy and immune checkpoint inhibitors in the treatment of cancer and the progress of interventional therapy combined with immune checkpoint inhibitors.

Immune checkpoints and cancer treatment

Role of immune checkpoints

Immune checkpoints are important regulators of immune activation and they play a key role in maintaining immune balance and preventing autoimmune diseases [8]. Activated T cells are the major mediators of immune effector function. T cells express multiple co-inhibitory receptors, such as lymphocyte-activation gene 3 (LAG 3), PD-1 and CTLA-4, which are used to regulate the responses of T cells to self proteins, chronic infections, and tumor antigens [8]. The action pathway of different immune checkpoint molecules is not the same.

Ctla-4

CTLA-4 plays a key role in the generation of peripheral immune tolerance to self proteins by neutralizing the function of CD28 [9]. CTLA-4 has a high affinity with B7 family molecules (about 20 times stronger than that of CD28) and can compete with CD28 to bind to B7 family molecules on antigen-presenting cells (APCs), blocking the signal transduction pathways of CD28 and B7, thereby inhibiting T cells activation [10]. CTLA-4 phosphorylates after binding to B7 protein, which in turn binds to phosphatidylinositol 3-kinase (PI3K), resulting in the activation of protein tyrosine phosphatase 2 (SHP2) and protein phosphatase 2A (PP2A) [9,11,12]. CTLA-4 interferes with T cell receptor (TCR) signaling by interacting with SHP2 and PP2A [8,13]. In addition, CTLA-4 can also acquire CD80 and CD86 molecules on APCs by trans-endocytosis, allowing them to degrade in cells expressing CTLA-4, which results in impaired co-stimulation via CD28 [14].

Although the activated $CD8^+$ effector T cells also express CTLA-4, CTLA-4 exerts its physiological functions mainly by decreasing the activity of $CD4^+$ T helper cells and enhancing the immunosuppressive activity of regulatory T cells (Tregs) [15]. Therefore, CTLA-4 inhibitors can both enhance the activity of $CD4^+$ effector T cells and inhibit the immunosuppressive function of Tregs, thereby enhancing the anti-tumor immune response.

PD-1/programmed death ligand 1, 2 (PD-L1, PD-L2)

PD-1 is mainly expressed on mature T cells and B cells, professional APCs and natural killer (NK) cells in peripheral tissues and tumor microenvironment. When tumor cells and APCs present tumor antigens to T cells and stimulate T cell activation, PD-1 expression on the surface of activated T cells can be induced [16]. Unlike CTLA-4, which regulates T cell activation in lymphoid organs, PD-1 mainly regulates the activity of effector T cells in peripheral tissues and tumor tissues. PD-1 has two ligands: PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273). PD-L1 is expressed on the surface of lymphocytes, epithelial cells, and endothelial cells induced by γ-interferon which is produced by T cells and NK cells; however, PD-L2 is mainly expressed on the surface of APCs induced by interleukin-4 [17,18]. When binding to its ligands, PD-1 inhibits the kinase involved in the activation of T cells via phosphatase SHP2 [19]. At the same time, binding of PD-1 to its ligands inhibits TCR termination signals and alters the contact time of T cells with APCs or target cells, resulting in immune tolerance [20]. Like CLTA-4, PD-1 is also highly expressed on Treg cells, and PD-1 enhances Treg cell expansion by binding to its ligands [21]. However, the interaction between receptors and ligands in the PD-1 system is complex and its mechanism in tumor immune tolerance has not yet been fully elucidated. Currently, it has been found that inhibiting the interaction between PD-1 and its ligands can block the transmission of inhibitory signals, inhibit the immunosuppressive tumor microenvironment, and restore the activity of effector T cells, which therefore enhance anti-tumor immune effects [22].

Other immune checkpoints

In addition to the above-mentioned classical immune checkpoints, a number of immune checkpoint pathways have been discovered with different mechanisms of action, such as LAG 3 and T cell immunoglobulin mucin 3 (Tim-3). LAG 3 (CD223) is a molecule that inhibits the function of lymphocytes and is mainly expressed on the surface of activated $CD4^+$, $CD8^+$ cells and NK cells [10]. LAG 3 specifically inhibits the function of $CD8^+$ effector T cells by binding to its ligand major histocompatibility complex (MHC) class II molecules and enhances the inhibitory activity of Treg cells [23,24]. As tumor-infiltrating lymphocytes simultaneously express LAG 3 and PD-1, their anti-tumor immune function is significantly reduced, and inhibition of both LAG 3 and PD-1 can reverse the depletion of lymphocytes, thereby enhancing the immune response [25,26]. Tim-3 is a type of glycoprotein with extracellular immunoglobulins and mucin domains, which is mainly expressed on the surface of activated T cells and in the tissues such as liver and small intestine. The galectin-9 which expresses on the surface of Treg cells is an important ligand of Tim-3, and interaction of the receptor and ligand can inhibit the T cell immune activity, which plays an important role in the tumor immunosuppressive microenvironment [27]. Tim-3 and PD-1 are co-expressed on the surface of $CD8^+$ tumor infiltrating T cells and significantly down-regulate the function of $CD8^+$ T cells. Therefore, blockade of Tim-3 can enhance the anti-tumor effect of PD-1 inhibitors [28].

Clinical application of immune checkpoint inhibitors

CTLA-4 inhibitors

Allison et al. first demonstrated in the mouse model that anti-CTLA-4 monoclonal antibodies could enhance the anti-tumor immune response, resulting in tumor regression and inhibiting the growth of newly inoculated tumors [29]. Since 2000, anti-CTLA-4 monoclonal antibodies have entered clinical development.

Phase I/II clinical trials have shown that Ipilimumab can effectively suppress the growth of some malignant tumors such as melanoma, renal cell carcinoma, prostate cancer, non-small cell lung cancer, ovarian cancer, and urothelial carcinoma [30–32]. A randomized controlled phase III clinical trial explored the efficacy of Ipilimumab in combination with a peptide vaccine (gp100) derived from melanoma-associated glycoprotein in the treatment of metastatic melanoma. The results showed that the median survival for the combined group was 10 months and the median survival for the Ipilimumab alone group was 10.1 months, while the median survival for the gp100 alone group was only 6.4 months. Compared with gp100 alone, Ipilimumab alone significantly reduced the risk of disease progression ($HR = 0.64$, $P < 0.001$), and improved overall response rate (10.9% vs 1.5%) and disease control rate (28.5% vs 11.0%). Follow-up results found that 1-year survival rate and 2-year survival rate in patients with Ipilimumab alone were 45.6% and 23.5%, which were significantly higher than those in gp100 group (25.3% and 13.7%, $P < 0.05$) [33]. Since results of the clinical trials confirmed that Ipilimumab can significantly prolong survival, it was approved by the FDA for the treatment of patients with advanced melanoma in March 2011.

Kirkwood et al. conducted a phase II clinical trial to evaluate the efficacy of Tremelimumab in refractory or recurrent melanoma. The results of this trial showed that the objective response rate of Tremelimumab was 6.6%, the duration of response was ≥170 days, the benefit rate was 21% (objective response and stable disease), and the median overall survival time was 10 months, suggesting that Tremelimumab had a certain therapeutic effect on melanoma [34]. Subsequently, a phase III clinical trial comparing the efficacy of Tremelimumab and conventional standard chemotherapy in unresectable

stage IIIc or IV melanoma showed that Tremelimumab did not significantly prolong the median survival compared with chemotherapy (12.6 months vs 10.7 months, HR = 0.88, P = 0.127). The objective response rates were similar in patients with either therapy (10.7% vs 9.8%), but response duration of Tremelimumab was significantly longer than that of standard chemotherapy (35.8 months vs 13.7 months, P = 0.0011) [35].

PD-1/PD-L1 or PD-L2 pathway inhibitors

In 2003, Chen Lieping et al. confirmed for the first time in mouse models of head and neck cancer that PD-L1 inhibitors could enhance the efficacy of T cell-mediated immunity and provided a new method for tumor immunotherapy [36]. Topalian et al. reported a large-scale phase I clinical trial of anti-PD-1 monoclonal antibody (BMS-936558, Nivolumab) in 2002. Among 236 patients whose efficacy was evaluated, the objective response rate was 18% (14/76) for non-small cell lung cancer, 28% (26/94) for melanoma, and 27% (9/33) for renal cell carcinoma, of which the response duration of 20 patients lasted at least one year. There was no objective response for colorectal cancer and castration-resistant prostate cancer. During the entire observation period, the incidence of grade 3 or 4 drug-related adverse events was 14%, and 3 patients died of pulmonary toxicity. Nine out of 25 patients with positive PD-L1 expression were found to have an objective response, while no other patients with negative PD-L1 expression had objective response (P = 0.006) [37]. Further studies of patients receiving PD-1 monoclonal antibody (Nivolumab) showed that the median survival of melanoma patients was 16.8 months, 1-year and 2-year survival rates were 62% and 43%, the objective response rate was 31%, the median response duration was 2 years, and about 16% of patients discontinued for reasons other than disease progression [38]; the median survival for patients with non-small cell lung cancer was 9.9 months, 1-year, 2-year and 3-year survival rates were 42%, 24% and 18%, respectively, with an objective response rate of 17%, a median response duration of 17 months, and the incidence of grade 3 or 4 treatment-related adverse events was 14%, the treatment-related mortality was 2% [39]; the median survival for renal cell carcinoma was 22.4 months, the 1-year, 2-year and 3-year survival rates were 71%, 48% and 44%, respectively, the objective response rate was 29%, the median duration of response was 12.9 months, and the incidence of grade 3 or 4 treatment-related adverse events was 18% [40]. In addition to Nivolumab, another PD-1 monoclonal antibody (Pembrolizumab) also achieved good efficacy in clinical trials. An open-label, multicenter, phase Ib clinical trial evaluated the efficacy of Pembrolizumab in the treatment of advanced melanoma. The results showed an objective response rate of 33%, a 12-month progression-free survival rate of 35%, and a median survival of 23 months, and grade 3 or 4 treatment-related adverse events occurred in 14% of patients in this group [41]. In addition, Pembrolizumab also had a good efficacy in the treatment of recurrent or metastatic head and neck squamous cell carcinoma, non-small cell lung cancer, and advanced urothelial carcinoma [42–45]. Pembrolizumab and Nivolumab were approved by the FDA for second-line treatment of advanced melanoma in September and December 2014, respectively. Since then, multiple indications of these two monoclonal antibodies including non-small cell lung cancer, renal cell carcinoma, head and neck cancer, and urothelial carcinoma were approved by the FDA.

The results of a multicenter, phase I clinical trial of anti-PD-L1 monoclonal antibodies were first reported in 2012. A total of 204 patients with different types of tumors including non-small cell lung cancer, melanoma, colorectal cancer, renal cell carcinoma, ovarian cancer, pancreatic cancer, gastric cancer, and breast cancer were included in the study. In patients with assessable results, the objective response rate was 10.2% (5/49) for non-small cell lung cancer, 17.3% (9/52) for melanoma, 11.8% (2/17) for renal cell carcinoma, and 5.9% (1/17) for ovarian cancer, of which eight patients had a response duration of at least one year. The incidence of grade 3 or 4 treatment-related adverse events in this group of patients was 9% [46].

Rosenberg et al. conducted a one-arm, multicenter, phase II clinical trial to assess the efficacy of Atezolizumab in the treatment of patients with locally advanced or metastatic urothelial carcinoma who progressed after platinum-based chemotherapy. The overall response rate was 15%, when classified based on the proportion of expression of PD-L1 positive immune cells in the tumor microenvironment, the objective response rate was 26% in IC2/3 (≥5%) group, and 18% in IC1/2/3 (≥1%) group. After a median follow-up of 11.7 months, 84% of patients (38/45) continued to respond. The incidence of grade 3 or 4 treatment-related adverse events was 16%. Grade 3 or 4 immune-mediated adverse events occurred in 5% of patients [47]. A multicenter, randomized, controlled phase III trial showed that Atezolizumab did not significantly prolong the survival of patients with platinum-based chemotherapy-resistant metastatic urothelial carcinoma compared with different chemotherapy regimens (vinflunine, paclitaxel, or docetaxel), but Atezolizumab was better tolerated [48]. A one-arm, multicenter, phase II trial evaluated the efficacy of Atezolizumab as first-line treatment in patients with locally advanced or metastatic urothelial carcinoma who were not suitable for platinum-based chemotherapy. After a median follow-up of 17.2 months, the objective response rate was 23%, with a complete response rate of 9%, a median progression-free survival time of 2.7 months, a median overall survival of 15.9 months, a treatment-related adverse event rate of 10%, and an immune-mediated adverse event rate of 14%. Atezolizumab could be used as first-line treatment for metastatic urothelial carcinoma due to its good efficacy and safety [49]. A multicenter, randomized, controlled phase III trial of Atezolizumab in the treatment of non-small cell lung cancer showed that Atezolizumab significantly prolonged the overall survival compared with docetaxel-based chemotherapy, regardless of whether the tumor expressed PD-L1 or the tumor tissue type was squamous cell carcinoma. The incidence of grade 3 or 4 treatment-related adverse events in the Atezolizumab group was lower (15% vs 43%) [50]. Atezolizumab was approved by the FDA in May and October 2016 for second-line treatment of urothelial cancer and non-small cell lung cancer, respectively.

Avelumab has shown good efficacy in the treatment of chemotherapy-resistant metastatic Merkel cell carcinoma and metastatic or recurrent non-small cell lung cancer. Kaufman et al. reported the results of a multicenter phase II clinical trial of Avelumab in the treatment of Merkel cell carcinoma. The study included a total of 88 patients with a median follow-up of 10.4 months, an objective response rate of 31.8%, and only 5% of patients had grade 3 treatment-related adverse events, the incidence of treatment-related severe adverse events was 6% [51]. Gulley et al. reported a multi-center phase I clinical trial of Avelumab for non-small cell lung cancer in May 2017. After a median follow-up of 8.8 months in 184 patients, 50% of patients were in stable disease and the objective response rate was 12%. The incidence of grade 3 and above treatment-related adverse events was 13%, and the incidence of treatment-related serious adverse events was 9% [52]. Following the FDA approval of Avenumb in March 2017 for the first-line treatment of Merkel cell carcinoma, Avelumab was also approved by the FDA for the second-line treatment of urothelial cancer in May of the same year.

Durvalumab is another anti-PD-L1 monoclonal antibody which has been approved for the second-line treatment of urothelial carcinoma by the FDA. A multicenter phase I/II clinical trial showed that the objective response rate in patients who received Durvalumab for advanced urothelial carcinoma was 31.0%, the objective response rate in the PD-L1 positive (≥25%) subgroup was 46.4%, while there was no objective response in the PD-L1 negative subgroup, and only 3.9% of patients had grade 3 treatment-related adverse events [53]. Another phase I/II clinical trial also evaluated the efficacy of Durvalumab as a second-line regimen in the treatment of locally advanced or metastatic urothelial carcinoma. A total of 191 patients were enrolled in this study with a median follow-up of 5.78 months. The objective response rate was 17.8%, the median progression-free survival was 1.5 months, the

median overall survival was 18.2 months, and the one-year survival rate was 55%. The incidence of grade 3 or 4 treatment-related adverse events was 6.8%, and 2.1% of patients suffered from grade 3 or 4 immune-mediated adverse events [54].

Novel immune checkpoint inhibitors

At present, some novel immune checkpoint inhibitors, such as antibodies targeting LAG 3 and Tim-3, are still in clinical trials. A multicenter, open phase I trial is evaluating TSR022 (Tesaro) alone or in combination with PD-1 antibodies in advanced or metastatic solid tumors. Another ongoing multicenter, open phase I-Ib/II clinical trial was designed to investigate the efficacy and safety of MBG453 (Novartis) alone and in combination with PDR001 (PD-1 monoclonal antibody) in the treatment of adult advanced malignancies. Currently, there are several companies conducting clinical trials of LAG 3 antibodies, including BMS 986016 by Bristol-Myers Squibb, REGN 3767 by Regenerative and Sanofi, and LAG525 by Novartis. These clinical trials are focusing on observing the efficacy of LAG 3 antibodies alone or in combination with PD-1 antibodies in the treatment of advanced malignant tumors including non-small cell lung cancer, renal cell carcinoma, gastric cancer, and glioma. No preliminary results are available from the above-mentioned clinical trials.

Combined immunotherapy of immune checkpoint inhibitors

Although monotherapy with immune checkpoint inhibitors has demonstrated promise in the treatment of cancer, recent studies have shown that combined use of immune checkpoint inhibitors with different mechanisms of action can achieve better efficacy [55]. A randomized, double-blind, phase III study compared the efficacy of Nivolumab alone, Nivolumab combined with Ipilimumab, and Ipilimumab alone in treating patients with metastatic melanoma. Compared with a median progression-free survival of 11.5 months (95% CI, 8.9–16.7) for Nivolumab combined with Ipilimumab, Ipilimumab alone had a median progression-free survival of 2.9 months (95% CI, 2.8–3.4) (HR: 0.42; 99.5% CI, 0.31–0.57; $P < 0.001$), and 6.9 months (95% CI, 4.3–9.5) for Nivolumab alone (HR: 0.57; 99.5 %CI, 0.43–0.76; $P < 0.001$). The incidence of grade 3 or 4 treatment-related adverse events was 16.3% in the Nivolumab group, 27.3% in the Ipilimumab group, and 55.0% in the combined therapy group [1]. Given that combined use of Nivolumab and Ipilimumab showed excellent efficacy in patients with advanced melanoma, the objective response rate and progression-free survival of the first-line treatment were better than those of monotherapy, and the 3-year overall survival was higher than that of Ipilimumab alone [2], the combination of Nivolumab and Ipilimumab has been approved by the FDA for first-line treatment of patients with advanced melanoma.

Hans J. Hammers et al. reported the results of a phase I clinical trial of Nivolumab combined with Ipilimumab in the treatment of metastatic renal cell carcinoma. The objective response rate of this group was 40.4%, and the two-year overall survival rate was 67.3% for Nivolumab (3 mg/kg) with Ipilimumab (1 mg/kg) and 69.6% for Nivolumab (1 mg/kg) with Ipilimumab (3 mg/kg), respectively. The incidence of grade 3 or 4 treatment-related adverse events was 38.3% (Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg) and 61.7% (Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg) [56]. The data from the CheckMate-142 study on Ipilimumab combined with Nivolumab in the treatment of patients with mismatch repair defects/microsatellite instability-high metastatic colorectal cancer was also published recently. The results from 119 patients showed that the objective response rate assessed by the investigator was 54.6% (95% CI: 45.2–63.8%), the complete response rate was 3.4%, the partial response rate was 51.3%, 12-week disease control occurred in 80% of patients (95% CI: 71.5–86.6%), 9-month and 12-month disease-free survival rate was 76% (95% CI: 67.0–82.7%) and 71% (95% CI: 61.4–78.7%), 9-month and 12-month overall survival rate was 87% (95% CI: 80.0–92.2%) and 85% (95% CI: 77.0–90.2%), respectively. The incidence of grade 3 or 4 treatment-related adverse events was 32%. The incidence of treatment-related severe adverse events was 23% [57]. Another multicenter, open, non-comparative, randomized phase II clinical study enrolled 85 patients, of which 43 patients received Nivolumab monotherapy, 42 patients received Nivolumab combined with Ipilimumab. In Nivolumab monotherapy group, the confirmed objective response rate was 5% (95% CI: 1–16%), the median progression-free survival was 1.7 months, the median overall survival was 10.7 months, grade 3 or 4 treatment-related adverse events occurred in 7% of patients. In the combination therapy group, the confirmed objective response rate was 16% (95% CI: 7–30%), the median progression-free survival 4.1 months, the median overall survival was 14.3 months, grade 3 or 4 treatment-related adverse events occurred in 14% of patients [58]. A multi-center phase I clinical trial showed that Nivolumab combined with Ipilimumab as first-line treatment of non-small cell lung cancer also demonstrated good clinical efficacy [59].

In addition to the combined use of PD-1 and CTLA-4 inhibitors, some clinical trials are investigating the efficacy of combined use of other immune checkpoint inhibitors. A dose-escalation phase I clinical trial compared the efficacy of Nivolumab with LAG-3 antibody (BMS-986016) and LAG-3 alone (BMS-986016) in the treatment of advanced solid tumors. A phase I clinical trial of Nivolumab or Ipilimumab in combination with Lirilumab (KIR monoclonal antibody) for treatment of advanced solid tumors is also underway. Some other phase I clinical trials are evaluating the safety of PD-1 monoclonal antibody (MEDI0680 (AMP-514)) combined with PD-L1 monoclonal antibody (Durvalumab), PD-1 monoclonal antibody (Pembrolizumab) combined with 4-1BB monoclonal antibody (PF-05082566) in the treatment of advanced tumors. Currently, two multicenter, randomized, open phase III clinical trials are evaluating the efficacy and safety of PD-L1 monoclonal antibody (Durvalumab) in combination with CTLA-4 monoclonal antibody (Tremelimumab) in the treatment of advanced non-small cell lung cancer and head and neck squamous cell carcinoma.

Although combined immunotherapy for advanced tumors achieved good clinical results, the incidence of treatment-related adverse events was high, which affected the life quality of patients.

Interventional therapy and immune regulation (Fig. 1, Table 1)

Transcatheter arterial chemoembolization (TACE)

Chemoembolization has been widely used in the treatment of various solid tumors and TACE remains the current standard of care for patients with intermediate-stage hepatocellular carcinoma [60]. At present, there are different opinions on the effects of chemoembolization on immune regulation. Tumor embolization treatment results in necrosis of the tumor tissue, which reduces the release of immunosuppressive factors and attenuates the inhibition to immune function [61]; and necrotic tumor tissue can activate systemic immune responses by altering peripheral immune cell phenotypes [62]. However, embolization also reduces the number of peripheral T helper cells, which weakens the anti-tumor immune response [61]. At the same time, embolization can induce a hypoxic microenvironment, which leads to the up-regulation of HIF-1α expression and increases the expression of PD-L1 on the surface of immune cells and tumor cells, resulting in immunosuppressive effects [63]. In addition, patients with hepatocellular carcinoma are mostly in the middle and late stages of diseases at the time of treatment, so it is difficult to achieve precise embolization of tumor blood vessels, which often damages the normal liver tissue, leading to decreased immune function.

Ablation

Ablation can not only lead to local coagulative necrosis in the tumor, but also produce a large number of tumor fragments that can induce anti-tumor immune responses [64]. Current researches suggest

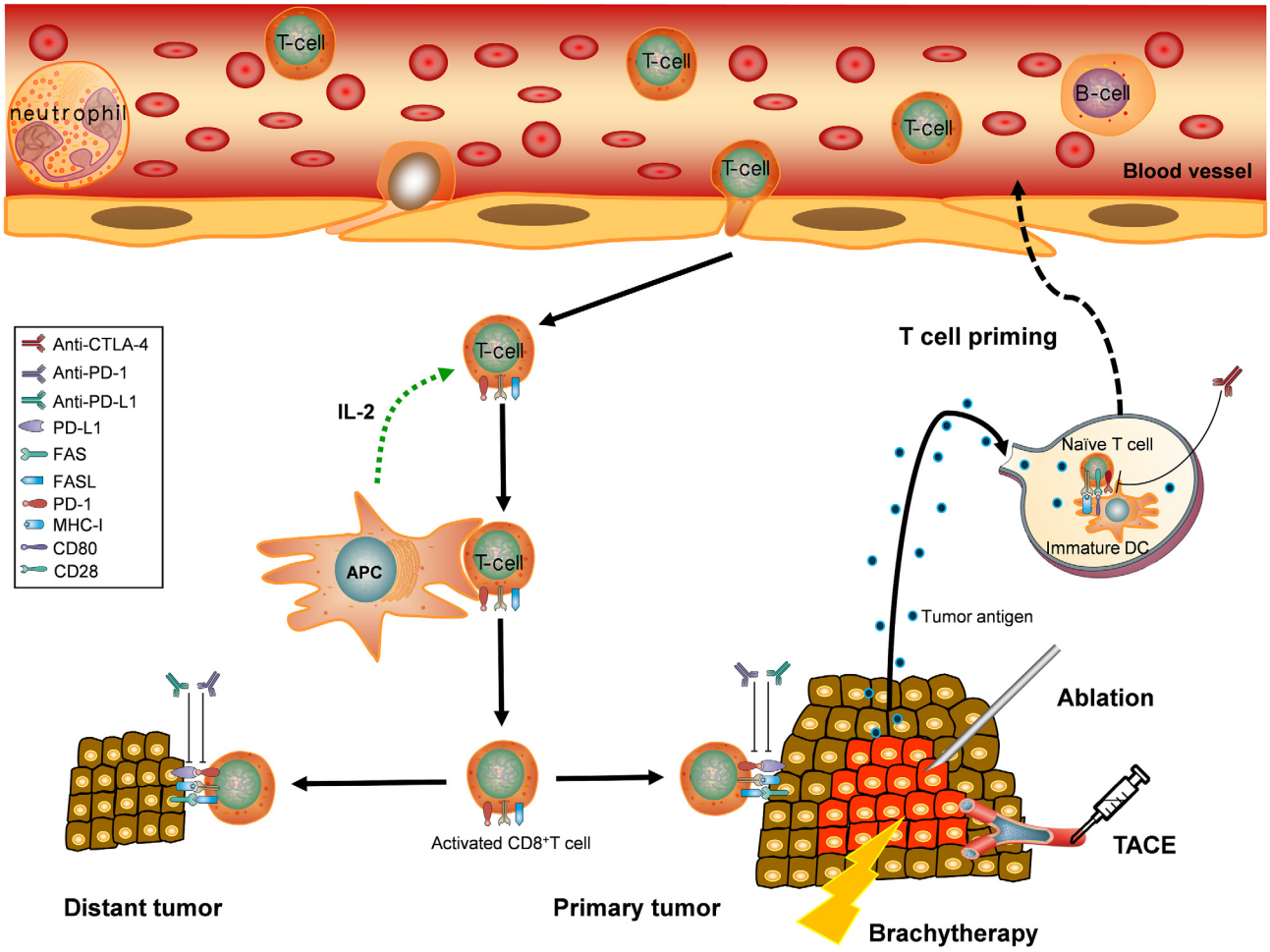

Fig. 1. Immune mechanisms triggered by tumor interventional therapy and potential immune checkpoint inhibitors that could be combined with interventional modalities. Interventional therapy, such as ablation, transcatheter arterial chemoembolization (TACE) and brachytherapy, can induce immunogenic stress or death of tumor cells and generate a large number of tumor antigens. At the same time, the above-mentioned process can induce strong inflammatory cell responses, which promotes dendritic cell (DC) maturation, upregulates costimulatory signals facilitating cross-priming of cytotoxic T lymphocytes (CTLs) and up-regulation of the corresponding chemokine receptors, thereby promoting the migration of DCs to the draining lymph nodes. DCs migrate to the lymph nodes and present tumor antigen peptides in major histocompatibility complex (MHC) molecules to T cells. T cells recognize these specific antigen peptides through T cell receptors. The co-stimulatory ligands CD80 and CD86 expressed on mature DCs bind to co-stimulatory receptor CD28 on the surface of T cells, stimulating the production of cytokines including IL-2 which is an important cytokine for T cell expansion; however, CD80 and CD86 can also bind to the co-inhibitory receptor cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), weakening the activation of T cells. T cells that are "educated" by the antigen leave the lymph nodes and "patrol" throughout the body to obtain tumor antigens. Effector T cells can home into both the treated primary tumors and lesions outside of the treated sites, resulting in the regression of distant tumors. Interventional therapy can increase the production of IL-6, HIF-1α, hepatocyte growth factor (HGF) and its receptor c-MET. These factors are closely associated with the expression and upregulation of some immune checkpoint proteins, especially programmed death ligand 1 (PD-L1). Antibodies against immune checkpoints, such as programmed cell death protein 1 (PD-1), PD-L1 and CTLA-4, can increase T cell activity directed against tumor cells, which has a synergistic effect in combination with interventional therapy.

that ablation can improve the anti-tumor immune response through the following mechanisms:

(1) Reduce immunosuppression: Ablation leads to regression and necrosis of the tumor, which reduces the tumor burden and decreases the release of immunosuppressive factors, thereby reducing the immunesuppressive effect on the immune system [7].
(2) Increase the exposure of tumor antigens: Ablation can destroy the tumor cell structure and expose a large number of tumor antigens, thereby enhancing the antigenicity of the tumor and playing a similar role as "in situ vaccine" [65].
(3) Enhance the immunogenicity of tumor antigens: Heat shock proteins (HSPs) are a type of polypeptide-binding protein, and there are several subtypes including HSP70, HSP90, and HSP96 (gp96). HSPs can be used as a carrier or peptide chaperone to combine with tumor antigens to form HSP complexes, which presents tumor antigens through the MHC I, and activates $CD4^+/CD8^+$ T cells to induce specific cellular immunity against tumor cells. Rai et al. found that radiofrequency ablation of tumor-bearing animals caused coagulation necrosis in the central region of the ablated lesions and HSP70 expression was significantly increased in peripheral non-fatal lesions [66]. The expression of HSP70 in the tissues of patients with hepatocellular carcinoma after radiofrequency ablation was 8 times higher than that before ablation. The high temperature could increase the expression of HSP70 and HSP90 in hepatoma cells, which enhanced the immune response to hepatocellular carcinoma [67,68].
(4) Activate APCs: DCs are known as the most powerful APCs. Mature DCs can activate antigen-specific T cells to kill tumors by presenting antigens and providing co-stimulatory signals to activate primary T lymphocytes and resting T lymphocytes. When tumor infiltrating DCs are insufficient or dysfunctional, tumor antigens cannot be

Table 1
The potential immune stimulation and suppression effects of interventional therapy.

Interventional techniques	Application examples	Potential mechanism(s)	
		Immune stimulation	Immune suppression
TACE	cTACE, DEB-TACE	① Result in necrosis of the tumor tissue; ② Reduce the release of immunosuppressive factors; ③ Alter peripheral immune cell phenotypes	① Reduce the number of peripheral T helper cells; ② Induce a hypoxic microenvironment; ③ Upregulate HIF-1α and PD-L1 expression; ④ Damage the normal liver tissue
Ablation	RFA, CA, MWA, IRE	① Reduce immunosuppression; ② Increase the exposure of tumor antigens; ③ Enhance the immunogenicity of tumor antigens; ④ Activate APCs; ⑤ Increase tumor-specific T cells	① Increase the production of IL-6, HIF-1α, HGF and its receptor c-MET; ② Upregulate PD-L1 expression
Brachytherapy	Iodine-125 seed, Yttrium-90 microsphere	①Induce in situ vaccination;②Reprogram the tumor microenvironment	① Increase the expression of PD-L1; ② Increase the infiltration of Treg into the tumor microenvironment

cTACE = conventional transcatheter arterial chemoembolization; DEB-TACE = drug-eluting bead transcatheter arterial chemoembolization; RFA = radiofrequency ablation; CA = cryoablation; MWA = microwave ablation; IRE = irreversible electroporation; APC = antigen-presenting cell; HGF = hepatocyte growth factor; HIF-1α = hypoxia-inducible factor 1α; PD-L1 = programmed death-ligand 1.

effectively presented to induce tumor-specific cytotoxic T-lymphocyte responses in the tumor [69]. Ablation can activate the DCs, thereby enhancing the antitumor effect of specific T cells [70].

(5) Increase tumor-specific T cells: $CD8^+$ T cells and natural killer cells are the main effector cells of tumor immunity and can directly kill tumor cells. After tumor ablation, a large number of tumor-specific $CD8^+$ T cells and natural killer T cells were accumulated in the border tissue of the necrotic lesions, further enhancing the specific anti-tumor effect [7].

However, ablation also has a certain role in tumorigenicity, namely the promotion of distant tumor growth and metastasis. Tumor ablation increases the production of IL-6, HIF-1α, hepatocyte growth factor (HGF) and its receptor c-MET [71–73]. These factors are closely associated with the expression and upregulation of some immune checkpoint proteins, especially PD-L1 [74,75]. Although studies suggest that local ablation can lead to systemic tumorigenic effects, it also provides a theoretical basis for ablation combined with immune checkpoint inhibitors in cancer treatment.

Brachytherapy

Brachytherapy, which is sometimes called internal radiation therapy, is a procedure that places radioactive material directly into or next to the tumor. Brachytherapy techniques are widely used in the treatment of various malignant diseases, such as Iodine-125 seed implantation of prostate cancer, radioembolization (Yttrium-90-labeled microspheres) of hepatocellular carcinoma or liver metastasis, irradiation stents loaded with Iodine-125 seeds for malignant biliary or airway obstruction, and some other tumors. Results from different studies have demonstrated that the efficacy of brachytherapy is either comparable to surgery and external radiotherapy, or improved when combined with the other modalities [76,77]. There is no research confirming the effect of brachytherapy on the immune system. However, studies on external radiation therapy have shown that radiation therapy can activate the immune response. Radiotherapy can not only destroy the irradiated tumors, but also result in the control of distant metastases outside of the localized treatment site, that is, the “abscopal effect” of radiotherapy [78]. The possible mechanisms involved in activation of anti-tumor immune responses due to radiotherapy are as follows:

(1) Radiation induces immunogenic stress or death of tumor cells, exposing the calreticulin (CRT) on the plasma membrane of tumor cells, and releasing adenosine triphosphate (ATP) and high mobility group box 1 protein (HMGB1). CRT, ATP and HMGB1 bind to CD91, P2RX7 and TLR4, respectively, and promote the recruitment of DCs into the tumor bed, the engulfment of tumor antigens, and optimal antigen presentation to T cells [79]. TLR4 activates the Myeloid differentiation primary response gene 88 (MyD88) signaling pathway, leading to translocation of NK-κB, which promotes maturation of DCs and upregulates MHC molecules and costimulatory ligands [80]. C3a and C5a released by complement activation via the alternative pathway are also very important for stimulating the maturation of DCs [81]. In conclusion, the above-mentioned process can induce strong inflammatory cell responses, which promotes dendritic cell maturation, upregulates costimulatory signals facilitating cross-priming of CTLs and up-regulation of the corresponding chemokine receptors, thereby promoting the migration of DCs to the draining lymph nodes. DCs migrate to the lymph nodes and present tumor antigen peptides in MHC molecules to T cells. T cells recognize these specific antigen peptides through T cell receptors. In the absence of costimulatory signals and cytokines released by DCs, the interaction of the MHC-peptide complex with the T cell receptor does not lead to T cell expansion, but instead results in T cell tolerance [82]. The co-stimulatory ligands CD80 and CD86 expressed on mature DCs bind to co-stimulatory receptor CD28 on the surface of T cells, stimulating the production of cytokines including IL-2 which is an important cytokine for T cell expansion; however, CD80 and CD86 can also bind to the co-inhibitory receptor CTLA-4, weakening the activation of T cells. Other co-stimulatory ligands that are up-regulated in mature DCs, such as ICAM-1 that binds to LFA-1 on the surface of T cells and CD40 ligands that binds to CD40 thereby playing an important role in activating $CD4^+$ T helper cells, help to activate $CD8^+$ T cells. T cells that are “educated” by the antigen leave the lymph nodes and “patrol” throughout the body to obtain tumor antigens. Effector T cells can home into both the irradiated tumors and lesions outside of the irradiated sites, resulting in the regression of distant tumors.

(2) Tumors can inhibit the anti-tumor immune response through a variety of mechanisms. Some tumors lack a suitable inflammatory mediator and therefore cannot effectively present antigens and produce tumor-reactive T cells. In addition, if the production of T-cell recruitment chemokines is reduced, T cells will not be able to accumulate within the tumor sites. Tumor blood vessels establish further barriers to tumor-reactive T cells by down-regulating adhesion molecules and expressing immunosuppressive ligands or death ligands. Under the influence of tumor and stromal derived inhibitory factors such as TGF-β, IL-10, and PGE-2, tumor endothelium can upregulate co-inhibitory ligands (TIM-3, PD-L1/PD-L2) and immunosuppression molecules (IDO-1, PGE-2), thereby

limiting the activation of effector T cells. T cells that successfully enter the tumor stroma may also encounter inhibitory immune cells such as activated macrophages (M2), MDSCs, and Tregs, which in turn cause T cell anergy, exhaustion, or apoptosis. Eventually, when T cells reach the target tumor cells, effective anti-tumor immune responses cannot be achieved due to the down-regulation of MHC molecules or tumor cell surface-specific tumor-associated antigens and the increased expression of immunosuppressive proteins such as PD-L1 on the surface of tumor cells. Radiotherapy can promote inflammatory responses by inducing expression of inflammatory mediators, IFN, and T cell chemokines. Radiation can convert tumor macrophages into type 1 macrophages (M1) expressing iNOS, and increase the expression of adhesion molecules ICAM-1 and VCAM-1 in tumor endothelial cells, facilitating the homing of T cells into tumors. Radiation also induces up-regulation of MHC I expression in tumor cells, allowing them to be recognized by the incoming T cells, which in turn releases effector cytokines to kill target tumor cells.

Radiotherapy can upregulate the expression of PD-L1 on the surface of tumor cells which was mediated by IFN-γ [83]. The expression of PD-1 was also reported to increase on tumor-infiltrating $CD8^+$ CTLs after radiotherapy. The upregulation of PD-1 or PD-L1 was regarded as one of the most important factors of radiation resistance [84]. Many other studies have shown that infiltration of Treg into the tumor microenvironment can be increased after radiation, which possibly resulted from the increased TGFβ secretion [85,86].

Application of combined interventional therapy with immune checkpoint inhibitors

The treatment of tumors against immune checkpoints is a research hotspot currently, however, there are still many deficiencies in monotherapy, for example, there is a limited population of overall benefits, and some tumors are not sensitive to immunotherapy. Combined treatment based on immune checkpoint inhibitors has become a new research hot topic, and interventional therapy combined with immune checkpoint inhibitors has shown promise in cancer treatment (Table 2).

TACE combined with immune checkpoint inhibitors

The outcome of TACE alone is poor and evidence from previous studies revealed that the tumor necrosis rate was only approximately 10–20% after TACE [87]. The addition of immune checkpoint inhibitors to TACE can increase the infiltration and improve the function of $CD8^+$T cells in the tumor microenvironment. The combination of TACE and immune checkpoint inhibitors can overcome the suppressive factors, such as PD-L1, induced by the hypoxic microenvironment after embolization. Thus, this combination category can enhance both local tumor control and systemic anti-tumor effect.

At present, there are many clinical studies on TACE combined with targeted drugs, however, TACE combined with different targeted drugs for treatment of hepatocellular carcinoma is not ideal. Meyer et al. reported the results of a randomized, placebo-controlled, double-blind, phase III clinical trial in which TACE plus sorafenib did not significantly prolong the progression-free survival of patients with hepatocellular carcinoma [88]. The ORIENTAL study conducted by Kudo et al. (a multicenter, randomized, double-blind, placebo-controlled, phase III clinical trial) showed that TACE combined with Orantinib demonstrated no significant improved overall survival in patients with unresectable hepatocellular carcinoma [89]. In another placebo-controlled, randomized, double-blind study using TACE in combination with Brifanib in patients with metastatic hepatocellular carcinoma, the study was terminated prematurely because the combination did not improve overall survival [90].

Phase I/II clinical trials have shown that immune checkpoint inhibitors have good efficacy in the treatment of hepatocellular carcinoma, and phase III clinical studies are still ongoing. TACE and immune checkpoint inhibitors may have a synergistic effect in treating tumors [91]. A clinical trial is evaluating whether TACE will enhance the clinical efficacy of CTLA-4 inhibitor (Tremelimumab) in the treatment of advanced hepatocellular carcinoma. Interim results showed that TACE combined with Tremelimumab is safe and feasible in the treatment of advanced hepatocellular carcinoma, and combination therapy could increase the infiltration of immune cells within the tumor site [92]. Guo et al. reported their experience of treating a case of small cell lung cancer with liver metastases. After receiving first-line chemotherapy, second-line chemotherapy, and radiotherapy, the condition was not effectively controlled. Then the patient was treated with TACE for liver metastases and four courses of immunotherapy based on Nivolumab, imaging studies showed continuous regression of liver lesions and stable lung lesions. The disease did not progress for 15 months. The authors concluded that TACE combined with Nivolumab could enhance the anti-tumor immune response and there was a synergy between these two treatment modalities [93].

Ablation therapy combined with immune checkpoint inhibitors

Animal experiments and human studies have shown that ablation therapy combined with immune checkpoint inhibitors can produce a synergistic local and systemic anti-tumor effect. When ablation is added to immune checkpoint inhibitors, the efficacy of immunotherapy against primary tumor or distant metastasis can be maximized with the help of a series of immune modulation mechanisms induced by ablation of tumors. Meanwhile, the blockade of immune checkpoint can counteract the immune suppressive effect of some factors which are closely associated with the overexpression of some immune checkpoint proteins, especially PD-L1.

The results of the mouse prostate cancer showed that cryoablation combined with CTLA-4 inhibitors had better therapeutic effects than cryoablation alone. Cryoablation of primary tumors had no effect on the growth of distant secondary tumors, while combination with CTLA-4 inhibitors could significantly slow the growth of secondary tumors and even eliminate secondary tumors. Compared with cryoablation alone, there was more cytotoxic T cell infiltration in the secondary tumors in the combination therapy group, and the ratio of cytotoxic T cells to Tregs was higher [94]. The results of mouse melanoma showed that radiofrequency ablation alone could only elicit a weak immune response, however, radiofrequency ablation combined with CTLA-4 inhibitors could produce a strong anti-tumor immune response and long-lasting tumor protection [64]. Compared with the monotherapy, radiofrequency ablation combined with PD-1 inhibitors could significantly inhibit tumor growth, prolong the duration of tumor growth inhibition, and prolong the survival in mice with colon cancer. At the same time, combination therapy could reverse immunosuppression in distant lesions [95].

Clinical trials found that ablation with CTLA-4 inhibitor (Tremelimumab) in the treatment of advanced hepatocellular carcinoma could enhance the accumulation of cytotoxic T lymphocytes in distant untreated lesions, increase the objective response of untreated lesions and extend the duration of response while effectively controlling primary lesions [96]. Bäcklund et al. reported a case of microwave ablation combined with Pembrolizumab in treating colorectal lung metastasis. After multiple surgical resections and stereotactic radiotherapy failed, the patient received microwave ablation combined with Pembrolizumab and had no signs of new lung lesions or tumor recurrence with eight months of follow-up [97]. Recently, Erik Soule et al. shared their experience of a case of metastatic renal cell carcinoma which was treated with percutaneous cryoablation and simultaneous local administration of Nivolumab. They found that the combined treatment could augment the systemic immune response against metastatic bone lesions [98].

Table 2
Reported clinical studies of interventional therapy in combination with immune checkpoint inhibitors.

Study	NO. of cases	Primary tumor	Histology	Metastatic site	Prior therapy	Type of interventional therapy	Type of immune checkpoint inhibitors	Immunotherapy regimen	Local response	Systemic response	Severe systemic adverse events
Bäcklund et al. [97]	1	Colorectal cancer	Adenocarcinoma	Lung	Chemotherapy, radiation, resection, multiple resections of lung metastases	MWA	Pembrolizumab (anti-PD-1)	Seven doses of pembrolizumab (standard dose with 2 mg/kg every third week)	The lung metastasis has not recurred	After 8 months of follow-up, there have been no signs of new or recurrent lung metastases	Neurological symptoms
Duffy et al. [96]	32	Liver	Hepatocellular cell carcinoma	All patients had evidence of progressive disease at enrollment	TACE, surgery, ablation, systemic chemotherapy, external beam radiation, 90Y radioembolization, sorafenib	RFA, CA or TACE	Tremelimumab (anti-CTLA-4)	At two dose levels (3.5 and 10 mg/kg IV) given every 4 weeks for a total of 6 doses, followed by 3-monthly infusions until off-treatment criteria were met	NR	PR 26% (5/19)	Hyperbilirubinemia (n = 3), aspartate aminotransferase increased (n = 7), alanine aminotransferase increased (n = 3), pruritus (n = 1), angioedema (n = 1)
Guo et al. [93]	1	Lung	Small cell lung cancer	Liver, mediastinal lymph nodes, adrenal gland	Irradiation, chemotherapy	TACE	Nivolumab(anti-PD-1)	3 mg/kg iv every two weeks , four doses	The liver lesion continued to decrease	No disease progression for 15 months	Myelosuppression
Soule et al. [98]	1	Kidney	Clear cell renal cell carcinoma	Bone	Chemotherapy naïve	CA	Nivolumab(anti-PD-1)	Nivolumab 40 mg suspended in 1 mL of Ethiodol was injected directly into the lesion	NR	Absent or dismissed uptake in the bone metastases as revealed in PET/CT; or the size of the lesion was slightly decreased with no change in form	None

ORR = objective response rate; CR = complete response; PR = partial response; PD = progressive disease; SD = stable disease; irDCR = immune-related disease control rate; PD-1 = programmed cell death protein 1; RFA = radiofrequency ablation; CA = cryoablation; MWA = Microwave ablation; TACE = transcatheter arterial chemoembolization; NR = not reported.

Brachytherapy combined with immune checkpoint inhibitors

Experimental studies have shown that after routine radiotherapy of mouse melanoma, colorectal cancer and triple negative breast cancer, the expression of PD-L1 in tumor cells increased, resulting in resistance to radiotherapy. Radiotherapy combined with PD-1 or PD-L1 inhibitors could enhance the anti-tumor specific T cell immune response, and meanwhile reduce the number of MDSCs in the tumor microenvironment and improve the therapeutic effect of radiotherapy [83,99].

Kwon et al. conducted a multicenter, randomized, double-blind, phase III clinical trial to evaluate the clinical efficacy of radiotherapy combined with Ipilimumab in the treatment of castration-resistant prostate cancer after chemotherapy resistance, compared with the placebo group, the overall survival did not extend in the group with Ipilimumab [100]. In another phase I clinical trial, 22 patients with metastatic melanoma received radiotherapy combined with Ipilimumab. Analysis of non-irradiated lesions showed partial response in 18% of patients and stable disease in 18% of patients. However, 64% of patients resisted to the combination therapy and the condition continued to progress. The authors further found that tumor cells would inhibit the proliferation and function of T cells by increasing the expression of PD-L1 after treatment of radiotherapy combined with CTLA-4 inhibitors, and radiotherapy combined with two immune checkpoint inhibitors with different mechanisms of action (CTLA-4 inhibitors + PD-1 or PD-L1 inhibitors) could significantly increase the complete response of mouse melanoma [101].

Radioembolization is a minimally invasive technique for the treatment of hepatocellular carcinoma that combines embolization and radiation. Radioactive isotope Y-90 microspheres were implanted into tumor-supplying blood vessels, resulting in high-dose radiation to the tumor. A phase I clinical trial is determining the maximum tolerated dose of Nivolumab in combination with Y-90 microspheres for advanced hepatocellular carcinoma and evaluating the effectiveness of this combination therapy. In addition, a phase II clinical trial is using Y-90 microspheres and Pembrolizumab to treat metastatic well-differentiated neuroendocrine tumors and metastatic hepatocellular carcinomas, which primarily focuses on evaluating the overall response rate of lesions outside the treated area.

Currently, there are few studies on the application of brachytherapy combined with immune checkpoint inhibitors in the treatment of tumors, but the relevant experience of external radiotherapy can be used for reference in brachytherapy.

Strategies of combined treatments

Even though interventional therapy combined with immune checkpoint inhibitors has achieved a series of success in some cases, how to combine these different treatment modalities is still on the exploratory stage. Currently, the popular strategy is interventional therapy followed by several intravenous doses of immune checkpoint inhibitors (Table 2), because there is a hypothesis that neoantigen-specific T cells induced by interventional therapy can improve response to immune checkpoint blockade. There was no consensus as to the dosage and frequency of immune checkpoint inhibitors when combined with interventional therapy. Most of the studies adopted the dosage regimens based on the experience of previous clinical trials on immune checkpoint inhibitors alone and adjusted them according to regular evaluation. As theoretical research is deficient, we are not sure whether the sequence of interventional therapy and administration of immune checkpoint blockade will cause different efficacy. There is still a long way to go before we develop a mature strategy of combined treatments.

Assessment of tumor response

Tumor response is an important indicator to evaluate the efficacy of different treatment modalities for solid tumors; consequently, it is crucial to develop validated and consistent criteria for defining response. The Response Evaluation Criteria in Solid Tumours (RECIST), which are simpler than the WHO response criteria, have been in widespread use in clinical trials of solid tumors. RECIST 1.1 were updated from the initially proposed RECIST and have been widely adopted to represent the standard criteria for response assessment currently. The classical RECIST only considered tumor shrinkage in terms of changes in size of tumor lesions as the sole measure of tumor response, hampering the proper assessment of response in hepatocellular cancer or liver metastasis. Thus, the concept of viable tumor according to intratumoral arterial enhancement on contrast-enhanced CT or MRI was introduced to amend RECIST to modified RECIST (mRECIST) [102].

With the widespread use of immune checkpoint inhibitors, the conventional evaluation of tumor response using criteria based on RECIST has been challenged, because RECIST were developed according to the mechanisms of cytotoxic drugs in treating advanced malignancies [103]. Several studies found that conventional RECIST might underestimate the benefit of immune checkpoint inhibitors in approximately 15% of patients [103–105]. Although some modified criteria, such as immune-related response criteria (irRC), immune-related RECIST (irRECIST) and modified RECIST1.1 for immune based therapeutics (iRECIST), were introduced to identify atypical responses in patients treated with immunotherapies, they were only applied in certain kinds of malignant tumors and they have not been determined if they are applicable in assessing response of interventional therapy combined with immune checkpoint inhibitors.

Potential side effects and complications

The combined treatments of interventional therapy and immune checkpoint inhibition are mostly safe and no severe complications as to interventional procedures were reported. However, the immune-related adverse events occurred frequently (Table 2), and the reported incidence is as high as 90% due to single-agent immune checkpoint inhibitors [106]. Although any organ system can be affected by the inhibition of immune checkpoints, the gastrointestinal tract, endocrine glands, skin, and liver are among the most common organs which are involved in the immune-related adverse events, whereas the immune-related adverse events much less frequently involve cardiovascular, hematologic, neurologic and ophthalmologic systems [107]. The majority of immune-related adverse events are not serious or life-threatening. Severe immune-related adverse events (grade 3 or 4) are reported to occur in up to 43% of patients with CTLA-4 inhibitors [106] and $\leq$20% of patients with anit-PD-1/PD-L1 antibodies [108].

Future directions

Interventional therapy combined with immune checkpoint inhibitors have opened up new areas for research in oncology treatment and have broad application prospects. However, related research is still in its infancy, and many key issues need to be resolved. First, when is the best time to combine interventional therapy with immune checkpoint inhibitors, and how should interventional therapy and immune checkpoint inhibitors be combined? There is no consensus on whether the interventional therapy and immunotherapy are performed at the same time or sequentially at present. Some studies suggest that interventional treatment leads to the release of tumor antigens and promotes antigen presentation, so there is an enhanced synergistic effect when interventional treatment and immunotherapy were performed simultaneously. However, the toxicity of the simultaneous treatment is greater, and sequential treatment can significantly reduce treatment-related adverse events. The interventional therapy-based local treatment can significantly decrease the primary tumor burden, and then adding immunotherapy, in theory, can enhance the anti-tumor immune response, thus preventing local recurrence and distant metastasis.

However, the immunomodulatory effects produced by some interventional treatments may be short-lived, and the timing of sequential treatment of immune checkpoint inhibitors needs further study. In addition, interventional therapy, immunotherapy, targeted therapy, radiotherapy and chemotherapy can be combined to achieve the best therapeutic effect. When two or more agents are combined with interventional therapy, the dosage of these agents might be cut because of their potential synergistic effect, which may reduce the treatment-related adverse events. Currently, relevant research is still relatively scarce, and the combination of multiple treatment modalities with different mechanisms of action may allow patients to benefit the most from the combined treatment.

Second, the toxic side effects of combination therapy remain important challenges. There are certain treatment-related toxicities existing in different combination treatment regimens, which seriously affect the quality of life and even endanger life. The methods for clinically treating treatment-related toxicities include active monitor, suspension of treatment, dose modification, and symptomatic treatment with steroids. There is still a lack of standardized treatment for treatment-related adverse events. The future direction should be to formulate a comprehensive assessment schedule, a joint treatment plan, and a clinical monitoring protocol based on the patients' overall condition to minimize or even avoid the occurrence of treatment-related toxic adverse events.

Finally, how to evaluate the efficacy of combination therapy. At present, most studies use the evaluation criteria of solid tumor efficacy (RECIST criteria) to evaluate the clinical efficacy of interventional therapy. The criteria are based on the size of the tumor and whether there is a new lesion to determine whether the disease progresses. However, studies have found that some patients have pseudo-progressive phenomena in the course of receiving immunotherapy. Therefore, the use of the RECIST criteria does not accurately assess the efficacy of treatment. Although evaluation criteria for the therapeutic effect of solid tumor immunotherapy has emerged, considering the complexities of interventional therapy combined with different immune checkpoint inhibitors, further clinical trials are needed to explore the therapeutic efficacy evaluation criteria for combination therapy.

Conclusions

Interventional treatment can reduce the tumor burden and regulate the immune response. There is a synergy between interventional therapy and immune checkpoint inhibitors to enhance the anti-tumor immune response. However, research of interventional therapy combined with immunotherapy is still in its infancy, and further studies are still needed to optimize treatment regimens to achieve the best effect of combination therapy.

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Declaration of interest

All authors declare that there are no conflicts of interest.

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