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ADVANCES IN CLINICAL RADIOLOGY

Interventional Radiology in the Era of Immuno-Oncology

Impact and Opportunity

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KEY POINTS

- Elucidation of the mechanisms involved in cancer's manipulation and evasion of the immune system has opened the door for new immunotherapy targets to promote an antitumor response.
- Two signaling pathways that have been extensively studied and used as treatment targets are B7-CD28, and programmed cell death 1 and programmed cell death 1 ligand.
- The profound immune response generated with locoregional therapies, may potentiate the effect of immune-modulating therapies, yielding synergistic treatment effects.
- Early results from combining locoregional and immunotherapies are promising, although prospective trials evaluating the clinical efficacy and survival benefit of combination therapy are needed.

INTRODUCTION

Decades of research have led to an improved understanding of the how the immune system targets and recognizes cancer and identifying key immune checkpoints to target as cancer treatment options. This knowledge has enabled the emergence of a new field, termed immuno-Oncology. In recent years, immunotherapies have radically reshaped cancer care and have demonstrated an expanding role in the management of oncology patients.

An in-depth knowledge of the underlying mechanisms that define the balance between stimulatory and immunosuppressive signals within the tumor microenvironment (TME) opens the door to seemingly endless targets for promotion an antitumor immunoresponse [1]. There are currently numerous commercially available cancer immunotherapies, which use this knowledge to target and inhibit key immunosuppressive checkpoints. These therapies have demonstrated clinical efficacy in more than 15 different types of cancer, including non–small cell lung cancer, squamous cell carcinoma of the head and neck, lymphoma, melanoma, and renal cell carcinoma [2]. A better understanding of the immune system's critical role in tumor detection and how cancer evades the immune system offers tremendous opportunity for interventional oncology.

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BACKGROUND

Immune System Function and Activation

The immune system is divided into innate and adaptive immunity. The innate immune system is the first line of defense against recognized pathogens; it provides a rapid inflammatory response and, perhaps more important, triggers the adaptive immune system. Adaptive immunity uses B and T cells to mount a sophisticated, pathogen-specific response and provide long-lasting protection [3]. The innate immune system links to adaptive immunity via the antigen-presenting cell (APC). A specific type of APC, the dendritic cell, circulates throughout tissues, constantly sampling and phagocytizing local antigens. In the setting of an activated innate immune system, dendritic cells are responsible for carrying those antigens to local lymph nodes, where they take place in antigen presentation to the awaiting T cells. A complex interaction of costimulatory and coinhibitory signals, determine whether antigen presentation will result in activation or inhibition of the T cell [3].

The population of T cells is mainly composed of helper, killer, and regulatory T cells. Immunosuppressive regulatory T cells, with the help of myeloid-derived suppressor cells (MDSCs), play a crucial role in self-recognition and immune tolerance, and help to avoid overstimulation [4]. This is accomplished, in part by downregulating cytotoxic, killer T cells. Cytotoxic, $CD8^+$ killer T cells are responsible for the cell-mediated death of virus-laden cells, as well as tumor cells [5]. Regulatory T cells and MDSCs have been shown to play key roles in maintaining tolerance of tumor-associated antigens and are thought to contribute to the progression of many tumors [4].

Key Checkpoints in The Immune Activation Pathway

Cytotoxic $CD8^+$ T cells are activated via a delicate balance of secondary costimulatory and coinhibitory interactions, which occur during antigen presentation. A particular costimulatory interaction between B7 and CD28 has been extensively studied over the years and has been shown to have great clinical impact. APCs express B7, which binds with high affinity to the CD28 receptor on the T cell during antigen presentation; this interaction results in a stimulation and activation of the T cell. These stimulatory signals are balanced by the inhibitory interaction with cytotoxic T-lymphocyte antigen-4 (CTLA-4), which competitively binds B7. Tight binding between CTLA-4, on the T cell, and B7, results in T-cell inhibition, favoring an immunosuppressive environment [6,7]. CTLA-4 inhibition may inhibit this immunosuppressive interaction and promote an inflammatory response. Monoclonal antibodies, targeted for inhibition of CTLA-4, have already gained US Food and Drug Administration approval for the treatment of several cancers, including ipilimumab for the treatment of unresectable melanoma [8].

Another immunosuppressive checkpoint that has developed a great deal of clinical relevance, is the interaction between programmed cell death 1 (PD-1), and its ligand, PD-1 ligand (PD-L1) [2]. PD-1, expressed on activated CD8+ cytotoxic T cells, exhibits a coinhibitory effect upon interaction with PD-L1. Interestingly, many types of cancer cells directly express PDL-1, which is thought to play a pivotal role in how these tumors evade the immune system [9]. PD-1/PD-L1 interaction prevents further T-cell activation and limits T-cell responsiveness. Prolonged PD-1/PD-L1 interaction has been shown to lead to T-cell exhaustion, resulting in the loss of cytotoxic function and decreased cytokine production. Several PD-1 and PD-L1 inhibitors are currently available and approved for use; for example, nivolumab, a PD-1 inhibitor, is currently used in the treatment of melanoma, non–small cell lung cancer, Hodgkin lymphoma, and renal cell carcinoma.

T-cell Exhaustion and The Tumor Microenvironment

T-cell exhaustion refers to a state of progressive dysfunction and eventual T-cell death. This hyporesponsive state is driven by chronic T-cell antigen exposure, such as tumor-associated antigens, without the appropriate balance of costimulatory factors [10]. Immune checkpoint proteins play crucial roles in the process of T-cell exhaustion; because exhausted T-cell are known to express high levels of inhibitory receptors, such as PD-1 and CTLA-4 [11,12]. Exhausted T cells may preserve the ability to recognize new antigens, although they do so in a state of relative quiescence. T-cell exhaustion may be overcome and even reversed by blockade of these overexpressed inhibitory receptors [13]. Although PD-1 inhibition has been shown to reverse T-cell exhaustion independently, several studies have brought to light the synergistic effects of simultaneous PD-1 and CTLA-4 inhibition, most notably in the setting of chronic hepatitis C infection [14]. In recent years, there has been increasing research and understanding of the complex mechanisms driving the immunosuppressive TME and its role in favoring T-cell exhaustion [2]. Tumor cells, along with several other cell types, including cancer-associated fibroblasts, with their associated extracellular matrix, induce a

localized immunosuppressive milieu. A unique population of tumor infiltrating lymphocytes, enriched by regulatory T cells and MDSCs, comprise a major component of the TME [15,16].

Stratification of patient's specific TME, as guidance for predicting which patients will respond to a particular immune checkpoint inhibiting agent, is already underway. Smyth and colleagues [17] have proposed a TME stratification system based on the presence of tumor-infiltrating lymphocytes and PD-1/PD-L1 overexpression to predict response to PD-1/PD-L1 inhibiting immunotherapy.

Role of the Regulatory T Cell

Regulatory T cells, a key subset of $CD4^+$ T cells, which play an important role in self-tolerance, have also been implemented in maintaining the immunosuppressive milieu of the TME. Regulatory T cells have been identified as early responders to tumor antigens and play a key role in early tumor growth and the downregulation of tumor-specific immune stimulation [18–20]. Prior studies have linked high concentrations of regulatory T-cell infiltration in tumor tissues with poor patient prognosis and decreased survival outcomes [19,21].

IMMUNOSUPPRESSIVE MECHANISMS IN THE LIVER

Liver-Specific Immune Surveillance

The liver is continuously exposed to a large amount of bloodborne antigens and plays an important role in immune surveillance. Nutrient-rich portal blood, flowing directly to the liver, may contain a wide array of immunogenic pathogen-derived molecules, or even whole, intact pathogens, which are usually directly translocated via the damaged gut epithelium [22]. The liver hosts several unique mechanisms to prevent an excessive immune response, as well as establishing and maintaining self-tolerance [23].

For example, the liver houses unique populations of APCs, mainly liver sinusoidal endothelial cells and Kupffer cells. These cells express high levels immunosuppressive proteins such as PD-L1. Furthermore, alterations in the expression of major histocompatibility complex, a protein required during antigen presentation, favor the expansion of regulatory T cells and induce "tolerance" of $CD8^+$ T cells [22,24,25]. Tolerogenic $CD8^+$ T cells seem to lose their cytokine-producing ability, and have demonstrated markedly reduced cytotoxicity [22].

Chronic Liver Inflammation and the Tumor Microenvironment of Hepatocellular Carcinoma

Prolonged liver inflammation, in the setting of chronic hepatitis, cirrhosis or steatosis, further promotes hepatic immunosuppression and T-cell exhaustion, partially via PD-1/PD-L1 upregulation. Prior studies have correlated increased PD-L1 expression on Kupffer cells and liver sinusoidal endothelial cells on biopsy samples of patients with chronic inflammatory liver disease [26]. Additionally, it has been demonstrated that high levels CTLA-4, IL-10, and transforming growth factor-β expression, and impaired antigen presentation all play contributory roles in maintaining the immunosuppressive hepatic environment [23].

In hepatocellular carcinoma (HCC), additional immunosuppressive mechanisms become activated to avoid immune system detection. Variable major histocompatibility complex expression, downregulation of costimulatory factors, and alterations in the postprocessing machinery necessary for antigen presentation to T cells have all been implemented in playing roles [23,27]. HCCs are commonly infiltrated not only by regulatory T cells, but also by hepatic stellate cells, which have the unique ability to induce T-cell apoptosis and secrete immune suppressive cytokines [23].

Intratumoral accumulation of regulatory T cells has been associated with disease progression and poor patient prognosis [27–29]. Furthermore, dysregulation of both PD-1 and CTLA-4 play key roles in the pathogenesis of HCC, and increased PD-1/PD-L1 expression has been correlated with increased HCC stage, disease progression, and poor patient prognosis [27]. Single agent PD-1/PD-L1 or CTLA-4 inhibition has not shown impressive clinical outcomes for HCC. Given the complexity of these mechanisms, it is logical to conclude that a dual-therapy/multimodality approach may demonstrate more profound clinical results.

IMMUNOTHERAPY AND LOCOREGIONAL THERAPIES

Locoregional therapies, including percutaneous ablation (either chemical or thermal) and transarterial therapies (mainly chemoembolization and radioembolization) offer a less invasive treatment option for unresectable HCC and hepatic metastases, such as those from colorectal carcinoma. Open surgical resection remains the mainstay of curative treatment for HCC; however, less than 30% of patients are surgical candidates at the time diagnosis [30]. In addition to causing necrosis of the

targeted tumor, it has been shown that locoregional therapies expose a large amount of tumor-specific antigens and induce a local and systemic immune response [30–32]. It has become widely hypothesized that concurrent immunotherapy and locoregional control may exert a synergistic effect and leverage the newly induced immune response to trigger systemic antitumor activity [33].

Thermal and Chemical Ablation

Percutaneous ablative techniques, including thermal and chemical ablation, offer minimally invasive therapy by means of local tissue destruction. Thermal ablation induces cellular lysis and coagulative necrosis either via controlled heating (as in radiofrequency ablation [RFA], microwave ablation, and laser ablation) or rapid cooling cycles, as with cryoablation [34].

The resulting cell membrane rupture releases large numbers of tumor antigens, as well as numerous proinflammatory cytokines, including heat shock proteins and tumor necrosis factor [32]. These immunogenic signals induce a local and systemic, T-cell–dependent immune proliferation and potentiation of antitumor immunity. However, these immune responses are insufficient to prevent tumor recurrence, because tumors have been shown to overcome this transient immune response. The exact mechanisms have yet to be defined, although an increased proportion of regulatory T cells within the tumor-infiltrating lymphocyte population and PD-1/PD-L1 and CTLA-4 upregulation are thought to play key roles [5,35,36].

In 2016, Shi and colleagues [35] analyzed surgically resected primary colorectal carcinoma specimens in patients who had received preoperative RFA of hepatic metastases. Their findings confirm the systemic immunologic response after ablation; the primary tumors of patients treated with preoperative RFA demonstrated not only increased number of tumor-infiltrating lymphocyte, but also a greater proportion of cytotoxic $CD8^+$ T cells within this population. In contrast, the primary tumors of those patient who received RFA, also demonstrated higher levels of PD-1 expression than those in the non-RFA group, indicating a partial shift toward an immunosuppressive TME.

Shi and colleagues [35] also used a murine colon cancer model to demonstrate the synergistic effects of RFA and anti–PD-1 therapy. They implemented a 4-arm approach, including no treatment, RFA alone, PD-1 inhibition alone, and RFA plus anti–PD-1 monoclonal antibodies. The mice treated with simultaneous RFA and PD-1 inhibition demonstrated the longest duration of tumor growth inhibition, as well as prolonged survival compared with either the monotherapy group or the no treatment arm.

Mizukoshi and colleagues [37] evaluated peripheral blood samples in patients both before and after HCC ablation. Patients who received RFA of the primary tumor demonstrated enhanced HCC-specific, tumor-associated antigen T cells, which was associated with recurrence free survival. Additionally, they found an inverse correlation between recurrence-free survival and immunosuppressive MDSC populations, further suggesting that additional immunologic inhibition of MDSCs may enhance tumor-specific T-cell responses [37].

Collectively, these data support the notion that thermal ablation induces a systemic antitumor immune response. However, monotherapy may be insufficient to sustain long-term tumor immunity and prevent recurrence [36]. Current data also suggest that simultaneous immune checkpoint inhibition, mainly via PD-1, PD-L1, and CTLA-4 blockage, may allow for a synergistic effect and mitigation of the systemic tumorigenic effects after ablation.

Concurrent ablation and immune checkpoint inhibition had been most extensively studies in animal models, although the results are promising for synergistic tumor responses. A murine prostate cancer model, treated with cryoablation of the primary tumor and concurrent CTLA-4 inhibition, concluded that the addition of CTLA-4 inhibition augments tumor immunity, halts growth, and even causes rejection of metastatic lesions [38].

Using a murine melanoma model, den Brok and colleagues [39] concluded that the coadministration of CTLA-4 inhibitors potentiated the immune response after RFA. The addition of anti–CTLA-4 monoclonal antibodies enhanced the relatively weak immune response triggered by RFA alone. The combination provided a prolonged and sustained immune response, indicating the synergistic effect of ablation and CTLA-4 inhibition.

Human trials are currently limited; however, tremelimumab, an anti–CTLA-4 monoclonal antibody, was studied as a combination treatment in patients with HCC who also received either ablation or chemoembolization. The results were promising, as the combination approach resulted in an objective and sustained tumor response of nontargeted tumors (ie, outside the ablations/embolization zone) [40].

Transarterial Therapies

Transarterial embolization seeks to leverage the arterial hypervascularity of hepatic tumors (mainly HCC and hepatic metastases) to achieve targeted delivery of the

embolic agent. Arterial embolization most commonly involves the delivery of a chemotherapeutic agent or radiopharmaceutical directly into the feeding artery. It is becoming increasingly accepted that an additional mechanism contributes to the efficacy of these procedures, involving systemic immunostimulation and the promotion of an antitumor response.

Similar to ablation, tissue necrosis and apoptosis achieved with transarterial therapies—mainly hepatic arterial embolization—has also been shown to release inflammatory cytokines and tumor antigens, which stimulate a systemic and tumor-specific T-cell response [41]. In contrast, embolization procedures have also been shown to upregulate hypoxia-inducible factor-1α, which has been associated with increased PD-1 expression, and poor prognosis in several human tumors [42,43].

Several prior studies have demonstrated a local and systemic tumor-specific immune response after transarterial embolization. For HCC, shifts in peripheral leukocyte populations have been demonstrated after hepatic arterial embolization, with expansion of peripheral neutrophils and decreased total lymphocytes. Perhaps more interestingly, this study also found a decreased proportion of inhibitory $CD4^+$ regulatory T cells in the circulating lymphocyte pool [44]. Additionally, an increase in alpha-fetoprotein–specific $CD4^+$ T cells has been observed after hepatic embolization [31]. This AFP alpha-fetoprotein–specific T-cell response was associated with clinical response to embolization, and demonstrated a dose–response relationship with tumor necrosis on pathology [31].

Radioembolization and Immunotherapy

Current data on immunomodulation after radioembolization are extremely limited. A recent study in 2018 by Chew and colleagues [45] analyzed surgically resected HCCs and peripheral blood samples of patients who underwent transarterial yttrium-90 radioembolization (TARE) before resection. They found that patients who had received pretreatment with TARE demonstrated enrichment in tumor infiltrating lymphocyte populations of $CD8^+$ T cells and natural killer T cells, whereas patients who did not receive preoperative TARE showed a higher percentage of immunosuppressive regulatory T cells. Furthermore, nonresponders and transient responders to TARE were found to have reduced levels of proinflammatory cytokines, including tumor necrosis factor-α and interferon-γ [45].

PD-1 and Tim-3 (another inhibitory checkpoint protein, associated with T-cell exhaustion) have been associated with tumor progression in HCC as well as in several other cancers. PD-1/Tim-3 coexpression may also be evidence of prior immune cell activation and suggest a prior antitumor immune response. In the study by Chew and colleagues [45], sustained responders were found to have increased levels of PD-1 and Tim-3 expression on T cells, before radioembolization, which persisted up to 6 months after the procedure. This led to the postulation that sequential blockage of both PD-1 and Tim-3, after TARE, may enhance a sustained clinical response for HCC patients.

Analysis of patient survival outcomes after concurrent treatment with TARE and immunotherapy is very limited in the current literature; to date, we are not aware of any randomized, controlled trials addressing this issue. A recent retrospective review of patients with metastatic uveal melanoma, who have had liver metastases treated with TARE and were also administered systemic PD-1 and/or CTLA-4 inhibitors demonstrated some promising results [46]. The overall survival of the group treated with immunotherapy and TARE was 33.5 months, as compared with prior reports of overall survival of 23.9 months after TARE alone [46,47]. These results are intriguing, although this retrospective review has several limitations and applicability concerns.

A preliminary case study, to be published November 2018, discusses a 32-year-old patient found to have a poorly differentiated, angioinvasive HCC [48]. He underwent treatment with concurrent TARE and nivolumab therapy. After 2 TARE treatments, 6 weeks apart, with concurrent biweekly nivolumab, there was a dramatic response on imaging, allowing for surgical resection via extended right hepatectomy. Histology demonstrated a complete pathologic response and no residual viable tumor. Although one should not draw strong conclusions from a single case study, these dramatic results are interesting and are further evidence that this treatment technique should be evaluated further.

Given the limited data currently available for alterations in the immune profile after radioembolization, results from radiotherapy studies could be extrapolated. The robust immune response after radiation therapy has been well-established. Radiation therapy has been shown to promote a systemic inflammatory response against tumor antigens, enhance APC function, overcome T-cell exhaustion, active cytotoxic $CD8^+$ T cells, and upregulate PD-1 [49–51].

The abscopal effect is a theoretic (albeit substantiated) phenomenon, of immune-medicated, systemic treatment response after local tumor treatment. The objective response of distant tumors, outside of the

targeted treatment zone, has been most commonly described after radiation therapy. There have been increasing incidences of documented abscorpal effect after combination radiation and immune therapies, resulting in complete or near-complete remission of disease [5].

FUTURE PERSPECTIVES

Early results from combining locoregional and checkpoint inhibiting immunotherapies are promising. There is a void in the literature of patient-centered, clinical outcomes for this synergistic approach to cancer therapy. There is a desperate need for prospective trials, for both ablation and transarterial therapies, to evaluate the clinical efficacy and survival benefit of combining these treatments with systemic immunotherapies. Before these trials could begin, a further elucidation of the local and systemic immunomodulation event that occurs after radioembolization would be helpful. Although there are promising data for the use of immune checkpoint inhibitors in cancer therapy, we have yet to tap into the full potential of combination treatments. In addition, there seems to a great deal of potential in evaluating the tumor response to dual target immunotherapy, such as concurrent PD-1 and CTLA-4 inhibition, and further studies are needed to evaluate these effects.

SUMMARY

An in-depth understanding of mechanisms involved in cancer's manipulation and evasion of the immune system has opened the door for the emergence of immuno-Oncology. The combination of locoregional and immunotherapy seem to house a great deal of untapped potential and, one day, may reshape our current understanding of cancer treatment. Many of the clinical trials addressing this issue are still in their early stages, although the next breakthrough treatment may be just around the corner. Interventional radiologists can benefit from understanding and adopting the use of immunotherapeutics to supplement and perhaps surpass the current efficacy of the locoregional therapies they perform on a regular basis.

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