

Biology

On the Immunotherapy for Tumors

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Tumor immunotherapy has made major strides in recent years, greatly enhancing the survival rate of cancer patients. Tumor vaccines, cellular immunotherapy, immunomodulatory medicines targeting T cells, immune checkpoint inhibitors (ICIs), and other forms of immunotherapy treatments have all developed one after the other. As new high-tech technologies emerge, tumor immunotherapy techniques are also continuously improved.

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TUMOR immunotherapy has made major strides in recent years, greatly enhancing the survival rate of cancer patients. Tumor vaccines, cellular immunotherapy, immuno-modulatory medicines targeting T cells, immune checkpoint inhibitors (ICIs), and other forms of immunotherapy treatments have all developed one after the other (1, 2). As new high-tech technologies emerge, tumor immunotherapy techniques are also continuously improved. This paper summarizes and reviews the advances in the field of tumor immunotherapy, describes the current state, difficulties, and combination therapies, and speculates on the future course of tumor immunotherapy.

The Status Quo of Tumor Immunotherapy

To treat various stages of cancer, immunomodulatory medicines that target T cells, cellular immunotherapy, tumor vaccines, and ICIs are gradually being used. Programed death ligand 1 (PD-L1) inhibitors are one of them and are used as representative ICIs (3). They have observed sustained responses and significant survival advantages in a variety of solid tumors and are approved for second-line or first-line treatment of a variety of tumors. The era of tumor immunotherapy has been ushered in by the active development of novel anti-tumor immunotherapies that target a

variety of targets and mechanisms. Examples include lymphocyte activation gene 3 (LAG-3) antagonists, CD3 immunomodulators, bispecific antibodies, chimeric antigen receptor (CAR)-T cell strategies, and customized neoantigen/cancer testis antigen nanovaccines.

The Difficulties of Immunotherapy for Tumors

Although tumor immunotherapy has made some ground-breaking achievements, there are still several obstacles in the way of the larger societal objective of “curing cancers.” On the one hand, tumors themselves are heterogeneous, complicated, and adaptable. On the other hand, immunotherapy mainly controls the tumor immune microenvironment, in which tumor cells interact with numerous non-tumor cells. Immunotherapy does not, however, target tumor cells individually. A complicated network of interactions is created, which has many different impacting elements.

Examining Prognostic Indicators of the Impact of Immunotherapy

The foundation of tumor immunotherapy in the era of precision medicine is biomarker discovery. Predictive biomarkers, such as tumor genomic markers, tumor immune microenvironment

markers, host germline genetic markers, transcriptomics and epigenetic markers, systemic blood circulation markers, and intestinal commensal flora, among others, have gained a deeper and more thorough understanding. Commonly utilized indicators of immunological effectiveness include PD-L1 expression, tumor mutation burden, microsatellite instability or mismatch repair gene abnormalities, tumor-infiltrating cells, and gut microbiota (4, 5). High sensitivity and specificity biomarkers have not been discovered yet, though. Because the regulatory mechanism governing immune response is often quite complicated, a single biomarker cannot accurately predict the benefit population and effectiveness of immunotherapy. Numerous biomarkers should be combined to create a quantitative prediction model to track the curative effect in clinical settings. Numerous biomarker strategies have developed as a result of the advancements in multiplex immunohistochemical technology, high-throughput DNA and RNA sequencing, and microarray technology, moving markers from being identified as single entities to being predicted by multiple factors working together (6). By combining elements such as pre-treatment normalized blood tumor mutational burden, circulating CD8+ T cells, and circulating tumor DNA dynamics, the researchers, for instance, used a Bayesian probabilistic model to construct an early, efficient, non-invasive identification of advanced non-small cell lung cancer (NSCLC) (7). Another researcher has developed a computational model of tumor immune dysfunction and rejection, which can be accessed through the website (<http://tide.dfci.harvard.edu>) to upload pre-treatment tumor sequencing data and get scores and efficacy prediction results. The DIREcTOn model, a biomarker model of durable clinical benefit after ICIs treatment in patients with non-small cell lung cancer (NSCLC), was developed by this researcher. It performs better than PD-L1, tumor mutation load, interferon, and other indicators in terms of first-line ICIs for treating melanoma. Combined detection can increase the ICI beneficiary population for independent predictive markers (8); for markers that interact, a comprehensive prediction model based on bioinformatics can be established in accordance with the various influence weights of each factor to increase the accuracy of screening beneficiary populations, which is more conducive to the formulation of tailored and accurate combined treatment approaches. Additionally, multivariate prediction models must combine many forms of data in accordance with various elements of tumor-host interactions and utilize machine deep learning or artificial intelligence to extract large-scale, multi-dimensional data features (9). Giving patients access to these revolutionary therapies will ultimately push the field toward precision immuno-oncology.

Overcoming Resistance to Immunotherapy for Tumors

Even though it is anticipated that tumor immunotherapy will have long-lasting effects, most patients will not benefit from it. Additionally, some initial responders may later develop adaptive or acquired drug resistance. Genes, metabolism, inflammation, and aberrant cell growth all play major roles in the mechanism. Neovascularization, along with a number of other factors, such as tumor intrinsic factors (such as tumor antigen loss or molecular defects in the process of antigen presentation, etc.), changes

in signaling pathways in tumor cells, and anti-tumor immune response pathways (tumor antigen loss or molecular defects in the process of antigen presentation, etc.), plays a role in the development of an inhibitory immune microenvironment (10). Tumor-extrinsic elements, such as the local tumor microenvironment and host-related elements, as well as many alterations in tumor cells. Immunotherapy-resistant populations can be quickly identified and excluded, new therapeutic targets can be found, and novel medications can be created with the aid of the gradual clarification and thorough investigation of immune resistance processes.

An Integrated Tumor Immunotherapy Approach

A potent way to boost or activate anti-tumor immune responses, get past medication resistance caused by many mechanisms, and ultimately beat cancer is to continuously investigate new and more potent therapeutic targets or combined tactics. In order to overcome medication resistance, corresponding actions should be taken in various immune response domains based on the characteristics of various immunophenotypes. Additionally, various action connections or targets and various combination strategies should be taken into account. Numerous unique combination tactics and cutting-edge treatment targets have emerged as a result of ongoing exploration.

ICIs in Combination with Chemoradiotherapy

Studies have indicated promise for immunotherapy, which is most frequently used in conjunction with traditional chemoradiotherapy. By releasing in situ vaccines, presenting antigens more effectively, removing an unfavorable tumor immune milieu, or encouraging tumor cells to express PD-L1, radiation might boost the systemic anticancer response to immunotherapy (11). Pembrolizumab and radiotherapy significantly improved median progression-free survival (PFS) and overall survival (OS), and no new safety issues were discovered, according to a pooled analysis of the encouraging PEMBRO-RT (Phase 2) and MDACC (Phase 1/2) trials (12). However, these findings need to be confirmed in randomized phase III trials. The clinical benefits of immunocombination chemotherapy can be expanded due to the ability of chemotherapy medications to directly or indirectly enhance immune responses and improve tumor immunogenicity (13, 14). Systemic chemotherapy has been demonstrated in certain trials to decrease B lymphocytes, although it has no discernible impact on T lymphocytes, NK cells, or other subsets. It is the preferred first-line treatment for patients with advanced NSCLC due to its significantly increased OS and PFS, therapeutic effects that cannot be matched by chemotherapy or immunotherapy alone, and tolerable toxicity (15).

Combination Therapy Strategies Using Dual ICIs

According to the Checkmate-227 research, Nivolumab, a PD-1 inhibitor, and ipilimumab, a cytotoxic T lymphocyte-associated antigen-4 inhibitor, significantly enhance the treatment of advanced NSCLC patients with PD-L1 tumor percentage scores below 1% (16). In the Checkmate-9LA study, the combination

of nivolumab, low-dose ipilimumab, and two cycles of concurrent chemotherapy lowered the risk of death by 31% and significantly extended OS by 15.6 months compared to chemotherapy alone (17). Targeting LAG-3, T cell immunoglobulin mucin molecule 3, T cell immunoglobulin and immunoreceptor tyrosine inhibitory motifs, as well as other potential inhibitory receptors or targets, including ligands related to the B7 family, such as antibodies like B7-H3, B7-H4, and B7-H5 (VISTA), are also constantly being developed (18, 19). Recently developed inhibitory receptor antibody combination therapy regimens include PD-1 inhibitor combined with anti-LAG-3 antibodies Relatlimab (BMS-986916) and LAG525 (IMP701), anti-PD-1 combined with T cell immunoglobulin Mucin 3 inhibitor (NCT03099109), and concurrently developed therapies that block LGA-3 and T cell immunoglobulin Mucin 3 or major histocompatibility complex II and LAG-3. Although the toxicity of the dual-immune combination therapy regimen is manageable, careful consideration should be given during the exploration process, and the risk of negative drug reactions should be calculated in a timely manner to avoid issues before they develop.

ICIs and an Immune Agonist Approach

Theoretically, combining PD-1 inhibitors with neurotrophic tyrosine kinase receptor (NTRK)-214, a CD122 agonist and precursor of IL-2, can achieve pleiotropic immune activation through the IL-2 pathway, preferentially activating particular anti-tumor T cells and NK cells, and increasing the expression of PD-1 on the cell surface (20). According to data from the PIVO-T02 study, NTRK-214 combined with nivolumab demonstrated good efficacy in the treatment of advanced solid tumors; the efficacy was seen regardless of the patients' pre-treatment PD-L1 and tumor-infiltrating lymphocyte status (21). Early clinical studies of pembrolizumab or atezolizumab in the treatment of advanced solid tumors are currently underway. Additionally, agonistic antibodies to CD27, CD40, OX40, GITR, and ICOS, among others, can be used in immunotherapy to target stimulatory checkpoint molecules and modify the tumor immune milieu (22).

Bispecific Antibody Treatment Methods

For multi-channel synergistic resistance, bispecific antibodies can bind to two separate antigens or epitopes at once. In recent study, the more extensively researched bifunctional fusion protein M7824 (MSB0011359C) has been found to simultaneously block PD-L1 and "capture" transforming growth factor (23). This allows it to more potently inhibit tumor growth and metastasis while reducing the complexity of drug side effects and clinical development. The first line INTRPIDLUNG037 investigation was started as a result of the positive clinical efficacy data from the study of M7824 in the second-line treatment of advanced NSCLC (NCT02517398, NCT03631706). A powerful and highly selective small molecule inhibitor of MNK1 and MNK2, Tomivosertib (eFT508) reduces the production of IL-6 and IL-8 as well as particular immune checkpoint receptors, such as PD-1 and LAG3; preclinical studies have shown this to be effective (24). In addition, Tomivosertib, which can also be used to treat patients with solid tumors after ICI resistance, is shown in the model to stimulate anti-tumor immune responses in

a T-cell-dependent way and to increase the effectiveness of checkpoint inhibitors (25). SHR-1701, KN046 and AK104, which target PD-L1/cytotoxic T lymphocyte-associated antigen-4, and A-337, which targets CD3/EpCAM, are only a few of the bispecific antibodies currently undergoing clinical trials.

Utilizing ICIs Along with an Anti-Angiogenic Medication Strategy

An essential component of the tumor immune microenvironment is abnormal tumor angiogenesis, which can contribute to tumor escape through a number of routes and cause immunosuppression. Immunological checkpoint blockage enhances vascular normalization by activating CD4+ T cells, whereas antiangiogenic medicines that block VEGF or antagonize VEGF signaling positively enhance immune effects (26). As a result, immune therapy and anti-angiogenic medications may have synergistic anti-tumor effects since tumor vasculature and immunity are regulated reciprocally. The FDA has approved the multi-target medication Axitinib in combination with avelumab or pembrolizumab for the first-line treatment of renal cell carcinoma; this is a breakthrough based on the JAVELIN Renal 101 study (27) and KEYNOTE-426 research (28). As a result of this advancement, the FDA authorized the use of the PD-L1 inhibitor atezolizumab in conjunction with the anti-angiogenic medication bevacizumab for the treatment of metastatic or unresectable hepatocellular carcinoma without the use of systemic therapy. This combination therapy is now the first immunotherapy used in the first-line treatment of liver cancer. Additionally, immune-combined anti-angiogenic therapy has been researched in different solid tumors and has demonstrated good anti-tumor activity. One example is the assessment of the VEGFR-2 antagonist ramucirumab combined with pembrolizumab in a variety of solid tumors. ICIs in combination with small molecule VEGFRK inhibitors (29), for example, ICIs in combination with Lenvatinib Phase III studies LEAP-006 (NCT03829319) and LEAP-007 (NCT03829332) are currently underway.

ICIs in Conjunction with a Customized Tumor Vaccination Strategy

Inducing stronger anti-tumor effects by the combined use of neoantigen-based personalized tumor vaccinations and ICIs is a useful way to treat "cold tumors" (30-32). For instance, anti-PD-1 antibodies can be coupled with allogeneic cell vaccines or autologous dendritic cell vaccines for prostate cancer; the NT-001 and NT-002 studies examined NEO-PV-01. In advanced NSCLC, the NT-001 study has demonstrated preliminary efficacy in terms of vaccination tolerance and anticancer activity when combined with ICIs and/or chemotherapy (33, 34). For the treatment of NSCLC, the phase I/II clinical study of the CIMAvax-EGF vaccine in combination with PD-1 inhibitor (NCT02955290) demonstrated promising results, and the phase II clinical trial was successfully completed (35). Additionally, a fresh approach based on RNA sequencing and whole exome sequencing was created.

Cellular Immunotherapy Coupled with ICIs

Mechanistically, adoptive cell treatment uses cells that have been isolated from the tumor itself or blood and modified in

vitro, whereas antibody-mediated checkpoint blockage needs a rather large mutational burden and the presence of tumor-infiltrating lymphocytes. Autologous lymphocytes with increased activity due to the expression of certain CARs, or T cell receptors, directed at the target antigen (36). Adoptive transfer of tumor-targeted T cells could therefore bridge the immunotherapy gap for patients whose tumors are less immunogenic or “non-inflammatory.” Additionally, research has demonstrated that blocking the PD-1 signaling pathway of CAR-T cells can increase their anti-tumor activity and function as well as their durability (37). NK cell function was enhanced and survival time was greatly extended in aggressive ovarian cancer animal models treated with PM21-NK cells and anti-PD-L1 therapy (38, 39). Advanced NSCLC patients treated with pembrolizumab and allogeneic NK cells had superior outcomes, and the levels of NK cells and helper T cell type 1 cytokines, such as IL-2, TNF- β , and interferon gamma, were significantly increased after treatment, and the survival outcomes of patients were significantly improved (40). Additionally, a randomized phase I/IIA clinical trial is studying SNK01, and the results of a novel, non-genetically modified, increased cytotoxic autologous NK cell treatment (41).

How to Carry Out Accurate Combination Therapy?

The options for combination therapy are expanding in variety as immunotherapy advances. Combination therapy is extremely difficult due to the potential for many mechanisms via which different medications may interact. Before combination therapy becomes the clinical norm, a number of issues need to be resolved, such as indications, the target patient population, the order of the combination medications, the dose, the efficacy evaluation standards, the prediction and management of treatment-related toxicity, the development of useful biomarkers, etc. Therefore, in clinical practice, it is still very difficult to implement an exact combination immunotherapy. Since the majority of immunocombination clinical trials are still ongoing, it is currently impossible to tell precisely which patients should follow which treatment strategy. Track the effectiveness of the treatment in real time and foresee the development of drug resistance. Furthermore, despite the vast number of clinical studies, it should be understood that successful clinical research is not always the result of promising methodologies; in other words, translating mechanisms into clinical practice is not always successful. Future studies should focus on finding ways to increase study success rates without squandering resources. Future immunotherapy research must continue to concentrate on more precise segmentation with the goal of identifying the optimal immunotherapy combination and population in terms of age, tumor stage, number of treatment lines, and biomarkers. It can

maximize immunotherapy’s anti-tumor effects while minimizing side effects, achieving true customized precision therapy.

Perspectives

Tumor immunotherapy is currently quite popular, and several clinical trials are being conducted on various methods. Future research will likely go in a few other major directions as well. Optimize clinical research endpoints and procedures first. New clinical trial techniques must be developed in order to quickly prioritize and quicken the development of immunotherapy regimens. The experimental “platform” consists of trials with umbrellas and baskets, etc. Second, the use of biomarker screening may be advantageous given the variety and complexity of current single-agent or combination immunotherapy regimens, as well as the ongoing development and advancement of multiplex immunohistochemical techniques, high-throughput sequencing, and microarray technologies. To combat medication resistance and significantly enhance patient treatment outcomes, the large patient group has emerged as a research trend. By extracting large samples and multi-dimensional features, using machine learning and big data analysis, and building a multivariate scoring model, it may be anticipated to obtain the most accurate and comprehensive biomarkers or models and build a new framework for precise tumor treatment. Third, in future research, serial sampling and longitudinal evaluation of tumor biopsies and peripheral blood sampling during treatment, combined with multi-factor comprehensive analysis to clarify the heterogeneity mechanism of drug resistance, or the use of new technologies like whole-genome sequencing, are all possible options. As a result, immunotherapy can be used to treat a wider variety of tumor types. The identification of distinctive drug resistance sites or subclones, such as single-cell sequencing or epigenetic analysis, will assist in uncovering novel targets and creating new medications. Additionally, the development of new drug delivery platforms, such as biofilm nano-drug delivery systems, can deliver various immunotherapy medications, such as cytokines, checkpoint inhibitors, agonistic antibodies, and tumor vaccines and so on to specific areas of the human body through a variety of different drug delivery methods exerting their effectiveness, such as the transport of nanoparticles to immune cells in vivo, the use of nanoparticles for in vitro T cell production, increasing the therapeutic impact while lowering side effects.

The optimal treatment strategy for each type of patient depends on the research areas of multi-drug combination therapy and multi-disciplinary cross-integration. To overcome these obstacles, basic scientists and clinicians must collaborate and pool their resources in order to gain a faster understanding of the intricate relationships between tumors and immunity, develop the best possible treatment options for cancer patients, and advance the tumor immunotherapy. ■

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