CANCER IMMUNOTHERAPY:
FUNDAMENTAL CONCEPTS AND EMERGING ROLE

ONCOLOGY PERSPECTIVE

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Immunotherapy has been under evaluation for more than a century, but only recently has it entered a renaissance phase with approval of multiple agents for the treatment of cancer. Now, immunotherapy stands poised to join with traditional modalities, including surgery, chemotherapy, radiation, and hormone therapy, as a pillar of cancer treatment. Importantly, immunotherapy is not a single entity but represents several types of treatments, including checkpoint inhibitors, monoclonal antibodies, growth factors, and therapeutic vaccines, with different approaches to boost or restore the ability of the immune system to fight cancer.

This monograph provides oncology healthcare professionals with an overview of the role of the immune system in cancer and describes how the various immunotherapies are designed to target cancer cells. This information is highly relevant to understanding immunotherapy and may improve outcomes of patients with cancer.

**Key Objectives**

After reading this monograph, healthcare professionals will further understand:

- The evidence supporting the immune system’s role in cancer and the characteristics of an immune response
- Several mechanisms of immunotherapy
- Treatment considerations of cancer immunotherapy
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THE IMMUNE SYSTEM'S ROLE IN CANCER

Hallmarks of Cancer Pathogenesis
Six traits common to most, if not all, cancers were identified in a landmark paper by Hanahan and Weinberg published in 2000. These hallmark traits reflect changes that normal cells must acquire to become malignant tumor cells. A recent update to this paper acknowledged that the immune system has a critical role in cancer pathogenesis. In particular, tumors have the ability to specifically evade the immune system, allowing cancers to grow and spread. The traits common to cancers are listed in Table 1.

Table 1. Hallmarks of Cancer Cells

| 1. Grow in the absence of growth signals |
| 2. Evade the normal signals that stop growth |
| 3. Evade the normal death signals that prevent proliferation of damaged cells |
| 4. Escape from an intrinsic signal that limits cell replication to a finite number |
| 5. Induce the formation of new blood vessels to feed themselves |
| 6. Acquire the ability to invade other tissues and spread throughout the body |
| 7. Change cellular metabolism to support proliferation of cancer cells |
| 8. Evade the immune system to avoid destruction |

The Immune System in Cancer: Clinical Evidence
A significant and growing body of scientific evidence substantiates the role of the immune system in battling cancer. Evidence has demonstrated that patients with compromised or suppressed immune function have an increased risk of cancer compared to individuals with intact immune systems. In particular, it has been shown that patients who have undergone organ transplantation and are chronically immunosuppressed to prevent transplant rejection have an increased incidence of several cancers (Figure 1). In patients who have undergone kidney transplantation, this increased cancer risk ranges from 2-fold for common tumors, like colon, lung, prostate, and breast, to greater than 20-fold for non-melanoma skin cancer, non-Hodgkin's lymphoma, and Kaposi's sarcoma compared to the general population with intact immune systems. A similar trend toward an increased cancer risk has been seen with patients who have
undergone liver or heart transplants.\textsuperscript{5,6} In addition, cancer rates are increased in human immunodeficiency virus (HIV)-infected individuals, and an estimated 40\% of all patients with acquired immune deficiency syndrome (AIDS) develop cancer during their lifetime.\textsuperscript{8} In several observational studies, the risk of malignancies in patients with AIDS increased as certain immune cell counts declined.\textsuperscript{9,10}

Furthermore, although somewhat controversial, the use of immunosuppressive agents, including biologics that block tumor necrosis factor, has been associated with an increased risk or incidence of certain cancers. In a large US observational study, the use of immunosuppressive biologic agents for the treatment of rheumatoid arthritis was associated with a significant 1.5-fold increase in the risk of non-melanoma skin cancer and a trend for increased risk of melanoma.\textsuperscript{11}

Additionally, intratumoral T cells, which are key mediators of cellular immunity, have been associated with increases in overall survival (OS) in different cancers.\textsuperscript{12-14} In a study in which tumor-infiltrating T cells were measured in tumor specimens obtained from patients with advanced ovarian carcinomas,\textsuperscript{12} patients with intratumoral T cells had significantly longer median OS (50.3 vs. 18.0 months) and higher 5-year OS (38.0\% vs. 4.5\%) compared with those having no intratumoral T cells ($P<0.001$) (Figure 2).\textsuperscript{12} In colorectal cancer, histopathologic methods that identify high levels of T cells in or around the tumor may be a better predictor of survival than histopathological methods used in the current staging system.\textsuperscript{13}

Taken together, these data support the importance of the involvement of the immune system in cancer.

![Figure 2. Immune Cells Within Tumors Predicts OS\textsuperscript{12}](image)

**Key Learnings**
- The immune system is recognized as having a critical role in controlling cancer. Studies have demonstrated that diminished immune system function was associated with an increased risk of cancer. Additionally, an association has been established between tumor-infiltrating T cells and increases in OS in various cancers.
Cancer and the Immune System: A Dynamic Relationship

The regulation of tumor growth represents a dynamic state, in which the immune system can either block tumor growth, development, and survival (i.e., immune protection) or may promote development of tumors (i.e., immune evasion). This process can be conceptualized by a seesaw that balances immune protection on one side with immune evasion on the other (Figure 3). There are 3 stages of this process known as the 3 E’s: elimination, equilibrium, and escape.

Elimination refers to the stage in which cancer cells are identified and effectively eliminated by the immune system. In this stage, the balance is shifted in favor of immune protection (Figure 3A).

The equilibrium phase is entered in the event that the immune system is not able to completely eliminate all cancer cells but can control or prevent further outgrowth. As a result, the tumor cells persist but are ultimately prevented from spreading by the actions of the immune system. In the equilibrium stage, the conceptual seesaw is balanced (Figure 3B). This stage is thought to be the longest of the 3 stages and may persist for many years.

The escape phase is characterized by the inability of the immune system to eliminate and control the outgrowth of cancer cells. This stage may occur as a result of immune system exhaustion or when cancer cells acquire phenotypic alterations, thereby allowing them to evade or avoid the immune system. In the escape stage, the conceptual seesaw tips in favor of immune evasion, leading to progressive disease (Figure 3C).

Key Learnings
- There is a dynamic relationship between the immune system and tumor cells. Normally, the immune system is capable of eliminating tumor cells. However, tumor cells use multiple evasion techniques to avoid the immune system.
Native Immune Response
Antigen presenting cells, or APCs, are specialized cells that recognize foreign antigens and present antigen fragments to T cells. Antigens are the molecules produced by microbes or foreign agents that bind to T cells and antibodies. The interaction between APCs and T cells activates the T cells (Figure 4). These activated T cells replicate and specialize to mount an attack on cells expressing the specific antigen. This specialization includes proliferation of target cells to kill cancer, the activation of additional immune cells and mediators to enhance the immune response, and the development of memory T cells that can rapidly respond upon re-exposure to the same antigen.

Characteristics of an Effective Immune Response
There are several key characteristics or features of an effective immune response that result in the ability of the body to protect against foreign antigens. These key characteristics or features include target specificity, trafficking, adaptability, and durability (memory). The most important characteristic of an effective immune response may be target specificity, which ensures that the immune response is targeted toward specific antigens. An example of immune response target specificity is demonstrated in the autoimmune disease, type 1 diabetes mellitus. In this disease, specific T cells recognize and destroy insulin-producing beta cells in the pancreatic islets of Langerhans, while sparing other islet sub-types. Target specificity prevents off-target effects to other cell types.

APCs interact with T cells to elicit a specific and enduring immune response. This immune response is thought to be critical to controlling cancer.

The second characteristic of an effective immune response is trafficking, which refers to the ability of activated immune cells to migrate to particular antigens throughout the entire body. As an example, upon infusion into a rodent model, naive T cells were detected exclusively in secondary lymphoid tissues, such as the spleen and lymph nodes, where they normally circulate scanning for antigen presentation by APCs. Following exposure to the target antigen (ovalbumin), T cells proliferated and the activated T cells migrated to the organs where the target antigen was localized, including the lungs, liver, intestines, and salivary glands.

Figure 4. Initiation of Immune Response: Key Components

Adapted from Abbas AK, et al.
The third characteristic of an effective immune response is target adaptability. Adaptability allows for an expanded immune response beyond the initially targeted antigen through processes called epitope and antigen spreading. Epitope spreading occurs when immune cells are able to generate an immune response to other epitopes or regions of the target antigen, whereas antigen spreading occurs when immune cells are able to generate an immune response to related antigens originating from the same cell.\(^7\)\(^{20}\) As shown in Figure 5, vaccination with a single peptide (corresponding to amino acids 611-626 of target antigen) elicits T-cell responses not only against the original peptide but also against 6 peptides in different regions of the same target antigen, reflecting the adaptability of the immune response.\(^7\)\(^{21}\)

The fourth characteristic of an effective immune response is durability or memory, the ability of T cells to recognize antigens over time.\(^7\) Immunologic memory allows for an expedited and durable immune response upon re-exposure to antigens.\(^7\) As shown in Figure 6, a smallpox-specific T-cell response remained detectable for many years after a single vaccination.\(^22\) Detectable immune responses were seen in 89% of patients who had been vaccinated 31 to 50 years earlier and in 52% of those vaccinated 51 to 75 years earlier.

These native immune functions are thought to apply to protection of the body against cancer.\(^7\)

**Key Learnings**
- APCs are the initiators of T-cell driven immune responses.
- An effective immune response includes the key characteristics or features of target specificity, trafficking, adaptability, and durability (memory).

**Figure 5. Adaptability**\(^{21}\)

**Figure 6. Durability (immune memory)**\(^{22}\)

Reprinted from Inderberg-Suso EM, et al.\(^{21}\)
The Renaissance of Immunotherapy

For more than a century, advancements in cancer immunotherapy have spread across several phases. In 1890, Coley developed the first cancer vaccine (based on bacterial toxins), which was shown to have benefit in patients with inoperable cancer. Driven by findings from Coley and others, researchers developed tumor-specific monoclonal antibodies in 1978. Interests soared in cancer immunotherapy, and the Enthusiasm Phase was born. However, the clinical benefit or promise of cancer immunotherapy did not reach initial expectations, thus ushering in the Skepticism Phase in 1985. Subsequently, in 1997 there was a resurgence of interest in cancer immunotherapy as a viable treatment option. This Renaissance Phase was initiated with a number of therapeutic advances in cancer immunotherapy that has resulted in important drug approvals.

Immunotherapy Approaches

The National Cancer Institute defines immunotherapy as “treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases.” Immunotherapy encompasses several different treatment approaches: tumor antigen–targeted monoclonal antibodies, immunological checkpoint inhibitors, cytokines, and therapeutic cancer vaccines. Each of these treatment types has a distinct mechanism of action; however, they all are designed to boost or restore immune function in some manner.

Monoclonal Antibodies

Tumor-specific monoclonal antibodies can elicit a direct or indirect immune response that leads to cell death. There are a variety of monoclonal antibodies and these work via different mechanisms of action to cause cell death (Figure 7A). Some of these mechanisms include blocking signaling pathways needed for tumor cell growth, triggering an immune-mediated cytotoxic response (eg, antigen-dependent cellular cytotoxicity), or blocking angiogenesis. Tumor-specific monoclonal antibodies have become part of the therapeutic repertoire in treating leukemia, breast, colorectal, and head and neck cancers after improving OS and progression-free survival in randomized, Phase 3 clinical trials. Response rates of 8%-10% have been observed when these are used as a single agent in advanced stage, heavily pretreated, and recurrent disease. These rates have increased to 30% when combined with traditional chemotherapy and/or radiotherapy.

Checkpoint Inhibitors

The immune system depends on multiple checkpoints or “immunological brakes” to avoid overactivation of the immune system on healthy cells. Tumor cells often take advantage of these checkpoints to escape detection by the immune system. CTLA-4 and PD-1 are checkpoints that have been studied as targets for cancer therapy (Figure 7B). CTLA-4 has been shown to be aberrantly upregulated and present on the surface of T cells in certain cancers, dampening T-cell activation in response to tumor cells. PD-1 is another immunologic checkpoint that has been found to be upregulated in certain tumors; it inhibits T-cell function contributing to the tumor’s ability to evade the immune system. Inhibiting a checkpoint (ie, “releasing the brakes”) on the immune system may enhance the antitumor T-cell response. This class of therapy has shown efficacy in cancer and clinical trials are ongoing.

Cytokines

Cytokines, such as interleukin-2 (IL-2) and interferon-α (IFN-α), stimulate a broad-based immune response as opposed to generating a targeted response to a specific antigen. As an example, IL-2 has numerous effects on the immune system and acts as a general T-cell growth factor. It does this by binding to receptors on the surface of T cells (Figure 7C). This binding stimulates the proliferation of T cells, continued cytokine production, and activation of multiple types of immune cells. It is interesting to note that high dose IL-2 therapy has been shown to lead to durable complete responses in a subset of patients (4%-6%) in renal cell carcinoma and melanoma. This suggests that for this subset of patients, IL-2 therapy is able to successfully manipulate the endogenous antitumor immune response.

Therapeutic Cancer Vaccines

Therapeutic cancer vaccines are designed to stimulate the patient’s own immune system against tumor antigens.
(Figure 7D). By triggering the immune system, therapeutic vaccines can initiate a durable antitumor response that can attack tumor cells and lead to improved survival. It is important to recognize, however, that therapeutic cancer vaccines differ from traditional preventative vaccines, such as those for various infectious diseases. Notably, the primary goal of a therapeutic cancer vaccine is NOT to prevent disease but to generate an active immune response against an existing cancer.

Some therapeutic cancer vaccines have contained a recombinant protein comprised of a tumor antigen and an immune cell activator. Once injected or infused, APCs process the antigen and then express antigenic fragments on their surface for presentation to the patient’s T cells. These activated APCs are able to interact with naive T cells in the initiation of a T-cell driven immune response, as described earlier.

Figure 7. Mechanism of Action of Immunotherapies

A) Monoclonal Antibodies

B) Checkpoint Inhibitors

C) Cytokines

D) Therapeutic Cancer Vaccines
Immunotherapy: Present and Future

Today, immunotherapy is an established treatment modality in oncology spanning numerous solid tumors and hematologic malignancies. The US Food and Drug Administration (FDA) has approved at least 12 monoclonal antibodies for use in cancer treatment, starting in the late 1990s. Besides these agents, the FDA has approved several cytokines, an immune checkpoint targeting agent, and a cancer vaccine. The future of immunotherapy looks very promising as numerous cancer vaccines and other immunotherapies are currently in advanced stages of clinical development.

Features of Immunotherapy

Depending on how they engage the patient’s immune system, immunotherapies can be classified in a number of ways, including whether they act in a passive or active manner, and/or whether they specifically target tumor antigens (Table 2).

<table>
<thead>
<tr>
<th>Active</th>
<th>Passive</th>
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<tbody>
<tr>
<td>Engages immune system</td>
<td>Enhances pre-existing immune response</td>
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<tr>
<td>Durable</td>
<td>Short-lived</td>
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Some examples:
- Therapeutic cancer vaccines
- mAbs
- Cytokines

Table 2. Features of Immunotherapy

mAbs, monoclonal antibodies.
Active immunotherapies are personalized.
Checkpoint inhibitors may have characteristics of both active and passive immunotherapies.
Immunotherapies may be tumor-antigen specific or non–tumor-antigen specific.

Immunotherapy can be further classified as non-specific and specific. Cytokines and non-specific adjuvants are examples that produce a wide range of antitumor effects. In contrast, most monoclonal antibodies used in immunotherapy produce a specific immune response to a target antigen. Similarly, active immunotherapy would also be classified as generating a specific tumor antigen response.

Key Learnings
- Immunotherapy is defined as a treatment designed to boost or restore the ability of the immune system to fight cancer, infections, and other diseases. Effective types of immunotherapy include monoclonal antibodies, checkpoint inhibitors, and cytokines. Each treatment works via different mechanisms and has varying levels of target specificity, but does not have the ability to generate durable responses through immune memory cells. Therapeutic cancer vaccines mimic key features of a patient’s natural immune response and can create a durable response.
CONSIDERATIONS OF IMMUNOTHERAPY

**Immunotherapy works differently than traditional cancer treatments (ie, chemotherapy); therefore, the response to immunotherapy cannot be measured with the same metrics.**

*Dynamics of Immunotherapy*

Immunotherapy may have the potential to continuously refine its effect on mutating cancer cells through the dynamic interplay between cancer and the immune system. As the immune system targets and lysed ever-mutating cancer cells, additional tumor antigens are able to be taken up by APCs, potentially activating a broader immune response. In the hypothetical example shown in Figure 8, vaccine-activated T cells that target a prostatic tumor attack and lyse tumor cells. This releases other tumor-associated antigens (such as prostate-specific membrane antigen [PSMA] or mucin-1 [MUC-1]), which may be taken up by APCs to subsequently activate additional T cells specific for those antigens. This dynamic process between the immune system and cancer may contribute to the different kinetics of response that immunotherapy has compared with traditional cancer therapy (ie, chemotherapy).

**Kinetics of Response to Immunotherapy**

Immunotherapy is associated with a delayed, but durable response that differs from the rapid, transient response of traditional chemotherapy. As an example, in metastatic castrate-resistant prostate cancer (mCRPC), chemotherapy can dramatically affect tumor growth rates during the active course of treatment. However, the tumor growth rate returns to its pretreatment value once chemotherapy is discontinued, reflecting the underlying tumor characteristics and the transient effect of traditional chemotherapy. In contrast, immunotherapy can induce immunologic memory and may change or boost the immune status of the patient, even after the course of immunotherapy has been completed. Because it may take several weeks or months to generate an effective immune response, immunotherapy may not necessarily cause a dramatic or immediate reduction in tumor burden or tumor-specific markers. However, it has been shown to ultimately prolong OS.

The differing immunotherapy response kinetics infer that biomarkers used to monitor the effects of traditional therapies may not always be appropriate. For example, prostate-specific antigen (PSA) is routinely used to monitor the effects of hormonal therapy in patients with prostate cancer. However, agents that slow tumor growth may not necessarily cause PSA reductions, and consequently changes in PSA levels may be

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**Figure 8. Dynamics of Immunotherapy**

Adapted from Gulley JL. [49]
The immune system has a critical role in controlling cancer. The Prostate Cancer Clinical Trials Working Group recommends expanding the focus from rising PSA levels to evaluating additional measures of disease progression (e.g., bone lesions, substantive pain, soft tissue lesions) to make decisions about when to stop a given therapy in advanced prostate cancer.

**Immunotherapy Treatment Considerations**

Based on the noted difference in timing and duration of response compared to traditional chemotherapy, it has been suggested that the relative efficacy of immunotherapy may be greater with a smaller tumor burden. This also suggests that improved treatment responses and outcomes may be expected at earlier stages of disease. In addition, evidence from clinical trials suggests that earlier use of immunotherapy in a patient with less compromised immunity has a better chance of effectively activating an immune response (Figure 9). For example, patients with metastatic cancer who received more rounds of chemotherapy or received a cycle of chemotherapy more recently were shown to mount a diminished magnitude of T-cell response following therapeutic vaccine.

Another consideration is the use of immunotherapy with traditional agents, as combination therapy is now standard for the treatment of many types of cancer to improve clinical outcomes. Immunotherapy offers an additional mechanistic approach, thereby raising the potential for synergy when used in combination with chemotherapy, radiation, and/or hormone therapy. Indeed, several monoclonal antibodies that bind to specific targets on cancer cells when added to chemotherapy have been shown to improve survival compared with chemotherapy alone. It may also be possible to rationally combine 2 types of immunotherapy based on complementary mechanisms of action, although proof of this approach remains to be shown.

**Key Learnings**

- Immunotherapy demonstrates an initial lag in effect; but may be able to slow tumor growth over time and prolong OS. Based on delayed response kinetics, it is suggested that immunotherapy may be more effective in patients with lower tumor burden. Because immunotherapy has a different mechanistic approach than traditional agents, immunotherapy may act synergistically with other therapies.

**SUMMARY**

The immune system has a critical role in controlling cancer. Key features of an effective immune response include specificity (which ensures an antigen-targeted response), trafficking (which enables antigen targeting throughout the body), adaptability (which allows for a response against related antigens), and durability (which allows for an expedited and long-lasting response upon re-exposure to the antigen). Over time, cancer cells develop mechanisms to escape control by the immune system, leading to progression of disease. Immunotherapy is designed to boost or restore the ability of the immune system to fight cancer. It shows delayed response kinetics compared with traditional cancer treatment modalities, but has led to increased OS in certain cancers. Future use and clinical trials should take into consideration that immunotherapies may elicit a better immune system response if used while the patient is still immunocompetent. In addition, immunotherapy can offer the potential for durable clinical effects and synergy with subsequent therapies.
REFERENCES


