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IMMUNOTHERAPY IN ONCOLOGY: PROGRESSION TO FIRST-LINE TREATMENT AND THERAPEUTIC COMBINATIONS

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ABSTRACT

Immunotherapy has emerged as a groundbreaking approach in oncology by leveraging the patient's immune system to specifically target and eliminate tumor cells. Unlike conventional chemotherapy, which directly attacks cancer cells, immunotherapy stimulates immune mechanisms to generate a durable and targeted anti-tumor response. Initially introduced as a second-line treatment for patients resistant to standard therapies, it has now been established as a first-line option in several malignancies, including melanoma and non-small cell lung cancer (NSCLC). This transition is supported by clinical trials demonstrating prolonged survival, reduced recurrence rates, and an improved safety profile compared to traditional treatments. Despite its success, challenges remain, particularly in terms of patient response variability and immune-related adverse events. To enhance treatment efficacy, combination strategies have been explored, integrating immunotherapy with chemotherapy, radiotherapy, and targeted therapies. These combinations have shown promising results by improving tumor response rates and overcoming resistance mechanisms. Additionally, emerging strategies such as neoadjuvant immunotherapy and the use of immune checkpoint inhibitors in combination with novel agents continue to reshape the therapeutic landscape of oncology. This review provides an overview of the evolution of immunotherapy in oncology, emphasizing its transition to first-line treatment, the benefits of combination approaches, and the challenges that remain in optimizing patient outcomes.

KEYWORDS: Immunotherapy, cancer treatment, immune checkpoint inhibitors, first-line therapy, therapeutic combinations, tumor microenvironment.

INTRODUCTION

Immunotherapy has revolutionized cancer treatment by stimulating the patient's immune system to combat cancer cells. Unlike chemotherapy, which directly targets tumor cells, immunotherapy mobilizes immune mechanisms to recognize and eliminate malignant cells. Its significance lies in its ability to generate a durable and specific response against tumors, marking a major advancement in oncology.

Initially reserved for patients who failed therapeutic options after the first line of treatment, immunotherapy is now widely used as a first-line treatment in numerous oncological indications. This transition highlights the effectiveness and long-lasting impact of these therapies. Moreover, the side effects of immunotherapy are generally better tolerated compared to chemotherapy, primarily due to the specificity of its action. However, the question arises as to whether combining immunotherapy with other treatments, such as chemotherapy or radiotherapy, can further improve clinical outcomes.

1. Role of Immunotherapy in Oncology Treatment

1.1 Indications for Immunotherapy

Immunotherapy is currently approved for several types of cancer, including melanoma, non-small cell lung cancer (NSCLC), renal carcinoma, and certain head and

neck cancers. Immune checkpoint inhibitors, such as anti-PD-1, anti-PD-L1, and anti-CTLA-4, are the main agents used in these treatments. These inhibitors block proteins that regulate T-cell activity, thereby enabling T cells to attack tumor cells.

The growing interest in immunotherapy has led to an increase in clinical trials aiming to expand its indications to other cancer types, including breast, pancreatic, and prostate cancers, which were previously considered less responsive to immunological approaches. These targeted therapies exploit the patient's immune mechanisms to more effectively combat cancer cells and have generated significant interest in oncology for their potential to offer alternatives or complements to traditional treatments like chemotherapy and radiotherapy.[1]

1.2 Transition from Second-Line to First-Line Therapy

Historically, immunotherapy was reserved for patients who had failed standard treatments such as chemotherapy or radiotherapy, positioning it as a second-line treatment. However, recent studies have shown that using immunotherapy in the first line, particularly for NSCLC and metastatic melanoma, provides significant clinical benefits, such as prolonged overall survival and reduced tumor recurrence. Consequently, immunotherapy has been promoted to a first-line treatment in several indications, altering the standards of cancer management.

- **Non-Small Cell Lung Cancer (NSCLC)**
  Results from the KEYNOTE-024 trial showed that pembrolizumab was associated with longer progression-free and overall survival, along with fewer treatment-related adverse events, compared to platinum-based chemotherapy in previously untreated advanced NSCLC patients with a PD-L1 tumor proportion score of 50% or higher.[2]
  Additionally, atezolizumab treatment led to significantly longer overall survival compared to platinum-based chemotherapy in NSCLC patients with high PD-L1 expression, regardless of histological type.[3]
- **Metastatic Melanoma**
  Nivolumab, alone or in combination with ipilimumab, significantly improved progression-free survival compared to ipilimumab in previously untreated metastatic melanoma patients. Results with the combination suggest complementary activity between PD-1 and CTLA-4 blockade, particularly in PD-L1-negative tumors.[4]

1.3 Immunotherapy in Neoadjuvant Treatment

Immunotherapy could be used in early stages of cancer as a neoadjuvant treatment. The NICHE-2 trial demonstrated its efficacy by utilizing immunotherapy prior to surgical operations to reduce tumor size. This study was conducted on patients with untreated colorectal cancer before surgery. Among the 107 patients tested, 95% experienced a reduction in tumor size by more than half, and in two-thirds of the patients, the primary tumor completely disappeared. The three-year survival outcomes of these patients following treatment are still under investigation.

Neoadjuvant immunotherapy (NI) requires a stronger immune response compared to adjuvant therapy, as it occurs when tumor cells are more prevalent.

During the annual meeting of the American Society of Clinical Oncology (ASCO) in June 2023, the interest in NI for solid tumors, particularly stage III melanomas, was highlighted.[5]

Preliminary results from the BELLINI trial provide further evidence of its potential. The use of NI in patients with triple-negative breast cancer who exhibited partial radiological responses resulted in complete or near-complete responses after just a few weeks of NI, and this was achieved without chemotherapy.

1.4 Safety and Tolerance of Immunotherapy

Compared to chemotherapy, immunotherapy has a more favorable tolerance profile. The most frequent adverse effects include autoimmune reactions, such as skin rashes, colitis, or hepatitis. However, these effects are generally well-managed with corticosteroids or other immunosuppressants, and their impact on patients' quality of life is less severe than the effects of chemotherapy, such as myelosuppression, nausea, and infections.

1.4.1 Safety of Immunotherapy

The side effects of immunotherapy are often considered better tolerated than those of chemotherapy, although each type of treatment presents specific risks. Immunotherapy works by stimulating the immune system, which can sometimes cause side effects related to hyperactivation of the immune system against healthy tissues. Common side effects include.

1. **Fatigue:** Frequent but generally moderate.
2. **Skin Reactions:** Rashes, pruritus (itching).
3. **Inflammations:** This can include inflammation of the lungs (pneumonitis), liver (hepatitis), intestines (colitis), and thyroid (thyroiditis).
4. **Flu-like Symptoms:** Fever, muscle aches, and chills.
5. **Endocrine Effects:** Dysfunction of the thyroid or other endocrine glands.

These effects are often manageable with corticosteroids or other immunosuppressive medications and are reversible once immunotherapy is discontinued or adjusted.[6]

1.4.2 General Tolerance Profile of Immunotherapy

Although immunotherapy is not without risks and some adverse effects can be severe, it is generally better tolerated and associated with an improved quality of life

compared to chemotherapy, due to its more targeted and often less systemic nature.

- **Reduced Systemic Toxicity:** Immunotherapy tends to act more specifically, affecting fewer healthy cells compared to chemotherapy.
- **Manageable and Reversible Effects:** Although side effects of immunotherapy, such as autoimmune inflammations, can be severe, they are often better controlled with timely interventions like corticosteroids and are reversible.
- **Quality of Life:** Patients undergoing immunotherapy often report a better quality of life compared to chemotherapy, with fewer debilitating daily side effects such as severe fatigue or persistent nausea.

In patients with advanced non-small cell lung cancer (NSCLC) and high expression of the PD-L1 protein, mono-immunotherapies or combinations of immunotherapies have extended survival compared to chemotherapy. The frequency of side effects may be lower with single-agent immunotherapies compared to chemotherapy. However, the frequency of side effects might not differ significantly between combination immunotherapies and chemotherapy.[7]

1.4.3 Adverse Effects of Combination Immunotherapy

The rate of adverse effects was higher in patients receiving combination therapy. Specifically, 53% of patients undergoing concurrent treatment experienced grade 3 or 4 treatment-related adverse effects, compared to 20% observed in patients treated with ipilimumab monotherapy.[8] Although combinations offer potential benefits, they can also lead to an increase in adverse effects, necessitating careful and personalized management for each patient. Optimizing immunotherapy combinations requires adjustments and further research to maximize clinical benefits while minimizing side effects.[9]

1.5 Monitoring and Efficacy of Immunotherapy

Monitoring patients on immunotherapy requires special attention, particularly for the early detection of autoimmune effects and the evaluation of tumor response. Unlike chemotherapy, where responses are often rapid, immunotherapy may induce delayed responses or even apparent initial progression before improvement (pseudo-progression). Nevertheless, the long-term efficacy of immunotherapy, particularly in metastatic cancers, has demonstrated durable clinical benefits in a subset of patients, making prolonged follow-up essential.

1.5.1 Monitoring Patients on Immunotherapy

- **Detection of Autoimmune Effects**
  Monitoring patients on immunotherapy requires rigorous surveillance to detect autoimmune effects associated with immune checkpoint inhibitors (ICIs). These effects, known as immune-related adverse events (irAEs), may appear in a delayed and prolonged manner, affecting various organs and systems. Early detection and appropriate management of these effects are crucial to prevent severe and irreversible complications. Thus, regular and multidisciplinary follow-up is indispensable to ensure patient safety and optimize the benefits of immunotherapy.[10]
- **Monitoring Tumor Response**
  Monitoring tumor response in patients treated with immunotherapy requires a meticulous and multidisciplinary approach. Unlike chemotherapy, immunotherapy can induce atypical responses, such as pseudo-progression, where tumors initially appear to increase in size before shrinking. Consequently, repeated imaging and biomarkers, combined with specific evaluation criteria for immunotherapy responses, such as iRECIST criteria, are essential to differentiate true progression from a delayed treatment response.[11]

1.5.2 - Response and Effectiveness of Immunotherapy Delayed Response and Pseudo-progression

Immune checkpoint inhibitors such as durvalumab have shown significant improvements in overall survival in patients with stage III NSCLC. However, delayed responses and pseudo-progression have been observed, making tumor response assessment more complex than with conventional treatments. Pseudo-progression, characterized by an apparent initial increase in tumor size followed by regression, requires careful monitoring and evaluation to avoid premature treatment discontinuation.[12]

Long-term Effectiveness

Long-term follow-up studies have shown that some patients treated with immune checkpoint inhibitors (ICIs) exhibited durable responses and prolonged survival, even after treatment cessation, suggesting that immunotherapy can induce immune memory capable of controlling the disease in the long term.[13]

2 - Combination of Immunotherapy and Other Treatments in Oncology

2.1 - Combination of Multiple Immunotherapy Agents

The combination of multiple immune therapeutic agents, such as anti-PD-1 and anti-CTLA-4, has shown enhanced efficacy in certain oncological indications, particularly in metastatic melanoma. This approach helps amplify the immune response, although the risk of side effects is also higher, such as immune-related toxicities. Clinical studies have demonstrated that this combination prolongs progression-free survival and improves overall response.

2.1.1 - Immunotherapy Combined with Anti-CTLA-4 and Anti-PD-1 in Metastatic Melanoma

The combination of nivolumab and ipilimumab has shown higher overall response rates and improved

survival in patients with metastatic melanoma without BRAF mutations compared to standard chemotherapy. In a phase 3 study, the 1-year survival rate was 72.9% with nivolumab compared to 42.1% with chemotherapy (dacarbazine). These results suggest that the combination of these two agents may effectively improve outcomes for patients with metastatic melanoma.[14]

2.1.2 - Immunotherapy Combined with LAG-3 and Anti-PD-1 in Metastatic Melanoma

Inhibition of two immune checkpoints, LAG-3 and PD-1, offered superior progression-free survival compared to PD-1 inhibition alone in patients with metastatic or unresectable melanoma who had not been previously treated. These results validate blocking LAG-3 in combination with PD-1 as a therapeutic strategy for melanoma patients and establish LAG-3 as the third immune checkpoint whose inhibition shows clinical benefit. These data reinforce the additional benefit of dual immune checkpoint inhibition compared to monotherapy, add another immune checkpoint combination to the therapeutic arsenal, and establish the relatlimab–nivolumab combination as a new potential treatment option for previously untreated patients with metastatic or unresectable melanoma. (Funded by Bristol Myers Squibb; RELATIVITY-047 ClinicalTrials.gov number, NCT03470922.)[15]

2.2 - Combination of Immunotherapy with Targeted Therapy

Targeted therapy focuses on specific mutations in tumor cells and can complement immunotherapy. For example, in renal cancer, the combination of PD-1 inhibitors with tyrosine kinase inhibitors (TKIs) has shown an improvement in overall survival compared to TKIs alone. The synergy between these treatments results from the ability of targeted therapy to disrupt the tumor environment, thereby facilitating the infiltration of immune cells activated by immunotherapy.

- **Combination of Immune Checkpoint Inhibitors and Targeted Therapy in Renal Carcinoma**
  The combination of the PD-1 inhibitor, nivolumab, with anti-CTLA-4, ipilimumab, offers superior efficacy compared to sunitinib in terms of overall survival and objective response in patients with advanced renal carcinoma.[16] Combinations with angiogenesis inhibitors have shown efficacy in various cancers, leading to FDA approvals, such as pembrolizumab with axitinib for advanced renal cancer. Studies show that tyrosine kinase inhibitors (TKIs) can modulate the immune microenvironment, thus influencing the response to immune checkpoint therapies (ICTs).

2.3 - Combination of Immunotherapy with Chemotherapy

The combination of immunotherapy with chemotherapy is an increasingly used first-line strategy, particularly in non-small cell lung cancer. Chemotherapy induces tumor immunogenicity by increasing antigen presentation and modifying the tumor microenvironment, thereby enhancing the effectiveness of immunotherapy. Clinical trials have shown that this combination improves progression-free survival compared to chemotherapy alone while remaining well-tolerated.

2.3.1 - Nivolumab Combined with Chemotherapy

In the Check Mate 648 trial, nivolumab combined with chemotherapy improved overall survival (OS) in patients with esophageal squamous cell carcinoma compared to chemotherapy alone. Similarly, the Check Mate 816 trial demonstrated that combining nivolumab with platinum-based chemotherapy increased event-free survival and complete pathological response in non-small cell lung cancer (NSCLC). However, the immunosuppressive effects of chemotherapy require further evaluation to optimize this combination.

2.3.2 - Combination of Pembrolizumab plus Chemotherapy versus Chemotherapy Alone in Previously Untreated Patients with Metastatic Non-Small Cell Lung Cancer

The results of the KEYNOTE-407 clinical trial showed that adding pembrolizumab to chemotherapy (carboplatin and paclitaxel or nab-paclitaxel) significantly improved overall survival in previously untreated patients with metastatic non-small cell lung cancer. The median survival was 15.9 months in the pembrolizumab-chemotherapy group versus 11.3 months in the chemotherapy-only group. Furthermore, pembrolizumab also prolonged progression-free survival compared to chemotherapy alone.[17]

2.4 - Combination of Immunotherapy with Radiotherapy

In addition to its direct cytotoxic effects on tumors, radiotherapy can also induce immune effects, thereby increasing the sensitivity of tumors to immunotherapy. The combination of radiotherapy with immune checkpoint inhibitors has been studied in various solid tumors, with promising results, particularly in lung cancer and rectal cancer. This combination not only helps control the tumor locally but also triggers a systemic immune response through the abscopal effect.

2.4.1 - Combination of Immune Checkpoint Inhibitors and Radiotherapy

Radiotherapy can enhance the effectiveness of immunotherapy through several mechanisms, including increasing the immunogenicity of tumors and triggering abscopal effects. Radiotherapy causes DNA damage in tumor cells, leading to the release of tumor antigens and other danger signals.

These antigens then stimulate the immune system, boosting the effectiveness of immunotherapy. Additionally, abscopal effects occur when radiotherapy of one tumor induces an immune response capable of targeting and destroying distant tumor cells, thereby

enhancing the effect of immunotherapy on non-irradiated tumors.[18]

2.4.2 - Combination of Radiotherapy and Immune Checkpoint Inhibition in Non-Small Cell Lung Cancer

Radiotherapy can improve the efficacy of immunotherapy by stimulating the immune response, leading to better disease control. Recent studies have shown that this combined approach can result in a more durable response to treatment and better patient selection for locally ablative therapies.[19]

Induction of Immune Response by Radiotherapy and Its Impact on Combined Therapies

Radiotherapy has a significant impact on the tumor microenvironment by increasing the infiltration of immune cells, particularly cytotoxic T cells. By damaging the DNA of tumor cells, radiotherapy causes the release of DNA fragments into the cytosol, which activates the STING (Stimulator of Interferon Genes) pathway and leads to the production of type I interferons. These interferons play a key role in recruiting and activating immune cells in the tumor region, thereby enhancing the response to immunotherapy. Consequently, the combination of radiotherapy with immune checkpoint inhibitors can amplify tumor cell destruction, leading to more effective clinical responses, including abscopal effects that contribute to the regression of distant tumors.[20]

Synergy between Radiotherapy and Immunotherapy in Colorectal Cancer

Radiotherapy can induce an antitumor immune response by modifying the tumor microenvironment, thereby enhancing the efficacy of immunotherapies. The abscopal effect, where radiotherapy targeting one tumor triggers a systemic immune response that also affects non-irradiated tumors, has been observed in various types of cancers. These synergistic interactions between radiotherapy and immunotherapy offer significant clinical benefits, leveraging the immunological effects of radiotherapy to stimulate a more robust and prolonged antitumor response.[21]

2.5 - Immunotherapy and Oncolytic Viruses

Oncolytic viruses (OVs) provide a unique approach by selectively proliferating in cancer cells, releasing specific antigens, and stimulating the immune response. Although the combination of T-VEC (an HSV-1-based OV) with anti-CTLA-4 has improved response rates, larger studies have not shown a significant survival benefit, necessitating further analysis to understand the lack of benefits despite observed responses.[22]

2.6 - Immunotherapy and Therapeutic Vaccines

A team from Inserm is conducting clinical trials of a vaccine in patients with metastatic non-small cell lung cancer. This vaccine, called UCPVax, consists of fragments of the telomerase protein, which is highly expressed by cancer cells, and is injected into the bloodstream. So far, in 80% of cases after three injections, an immune response has been observed, and 50% of these patients have seen an extension in survival.[23]

CONCLUSION

Immunotherapy has significantly changed cancer treatment, with a gradual shift from second-line to first-line therapy in several indications. The better-tolerated side effects and long-term clinical outcomes make it a promising alternative to conventional chemotherapy. The future of immunotherapy also lies in its combination with other treatments, such as chemotherapy, radiotherapy, and targeted therapies, enabling the optimization of tumor responses while improving patients' quality of life. The continued exploration of these combinations and the expansion of therapeutic indications will continue to transform oncology in the coming years.

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