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REVIEW

Cancer Immunotherapy: A Breakthrough in Patient Care

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Abstract

Cancer is one of the world's leading causes of death. Conventional therapies, such as surgical resection, radiotherapy, and chemotherapy, have improved patient management and have shown overwhelming progress. However, the incidence and mortality rates among cancer patients are still extremely high, at approximately 20,5% and 10,6% for both sexes, respectively. This may be due to the heterogeneity of tumors, their special microenvironment, and the development of resistance to certain conventional therapies.

The concept of immunotherapy provided a new perspective on patient treatment. The interaction of tumor cells with their microenvironment depends on different factors and conditions that promote tumor proliferation or elimination. Immune cells are part of the tumor microenvironment and, in some instances, have been shown to be unable to kill tumor cells, allowing cancer cells to survive, grow and metastasize. This results consequently in poor patient outcomes. Here, we focus on how immunotherapy enables a significant reappropriation of the host's immune defense against cancer and how this therapeutic strategy has been incredibly beneficial in managing patients, especially those for whom standard therapies are ineffective.

Keywords: Cancer, Immune system, Immunotherapy, Survival rate

1. Introduction

Long regarded as a distinct and separate entity, tumor cells are part of a contexture that is slightly more complex. The assumption that the genetic component alone defines the genesis and promotion of cancer cells has evolved over time. With recent scientific discoveries, only 5−10% of all cancers are attributable to genetic alterations [1−3]. Several biological factors may contribute to tumor cell pathogenesis such as tolerance or failure of the immune system/immune cells and promotion of uncontrolled inflammation by the tumor [4−6].

The etiology of cancer has a tremendous influence on patient management. Chemotherapy, whether palliative, neoadjuvant, adjuvant, or curative, primarily aims to eliminate tumor cells using cytotoxic agents that interfere with cell proliferation and differentiation, which are the prerogative of cancer cells [7,8]. These cytotoxic compounds are involved at different biological and molecular levels, such as alkylating agents like carboplatin and cisplatin, which hinder DNA replication and transcription within the cell [7,9]. Radiation therapy has also brought several significant benefits to patient care [10]. The bombardment of cells by electromagnetic and particulate radiation has been reported to cause cell and DNA damage, thus facilitating tumor cell death or apoptosis [10,11]. These two therapeutic methods,

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combined with surgery, have profoundly contributed to improvements in patient survival over the past decade. In addition, chemotherapy, especially neoadjuvant chemotherapy consisting of 1−3 drugs [singlet, doublet, and triplet chemotherapy], has been shown to have promising results in high-grade, high-stage and metastatic patients [12−21]. Studies have revealed increased survival benefits for patients who received radiation therapy compared to non-exposed radiotherapy patients in several cancers [22−28]. While recognizing the contribution of these therapeutic strategies to the management of patients, it must be noted that they unfortunately face numerous limitations and side effects, inter alia, cytotoxicity of normal cells, resistance of cancer cells to drug/radiation administration, and long-term sequelae [29−33]. A renewal of how to address cancer therapies beyond the genetic component and the vision of cancer cells as distinct entity is required. Therefore, immunotherapy is complementary to traditional therapies and provides a new perspective for managing patients. Cancer cells are in close collaboration with their environment, namely, infiltrating and resident host cells, secreted inflammatory mediators or molecules, stromal cells, and the extracellular matrix, all of which form the tumor microenvironment (TME) [34,35]. Under certain conditions, the ability of effector immune cells to eliminate cancer cells and interrupt tumor progression is undermined by various mechanisms implemented by cancer cells. By stimulating the immune response or inhibiting these mechanisms via immunotherapy, it is possible to significantly contribute to tumor elimination and improve patient treatment [36,37]. In the present review, we will shed light on how immunotherapy enables a significant reappropriation of the host's immune defense against cancer and how this therapeutic strategy has been incredibly beneficial to the management of patients, especially those for whom standard therapies are ineffective.

2. Review Method

A concise review of the literature was conducted by considering articles and data directly relevant to our topic. Different keywords were selected namely "*Cancer*", "*Immunotherapy*", "*patients survival rate*," "*Immunotherapy success rate*." Filters were provided by some databases such as "*Web of science* ", "*Google scholar*" in order to retain the more relevant articles. Information was gathered by searching for clinical trial codes on the Food and Drug Administration website (https://www.fda.gov/).

3. Cancer immunotherapy: an ingenious therapeutic strategy

The immune system is a vast network of molecules, cells, and organs involved in the recognition and elimination of non-self/altered self-entities [38,38,39]. Cancer cells can result from genetic alterations and mutations in genes related to cell growth and proliferation mechanisms [40,41]. These mutations initially occur in normal and healthy cells, making tumor cell components of the altered self [42,43]. Under these circumstances, innate and adaptive immune cells should be able to identify and clear tumor cells via immunosurveillance. Regrettably, cancer cells have developed many strategies to evade immune cell responses, including immune cells exhaustion through immune checkpoints (ICs) [44−46]. Immune-checkpoints are molecules present on the surface of both immune cells and cancer cells as receptors or in a soluble form [47]. Binding to their ligands that are usually expressed either on antigen-presenting cells (APCs) or cancer cells, activates pro-inflammatory or anti-inflammatory signaling pathways that lead to the regulation of the immune system [48]. The discovery of Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) and Programmed Cell Death Protein 1 (PD-1) by Pierre Golstein in 1987 and Tasuku Honjo in 1992, respectively, has led to further understanding of their involvement in cancer treatment [49,50]. This milestone marked the beginning of a new era, "the era of cancer immunotherapy," in which James P. Allison and Tasuku Honjo were jointly awarded the 2018 Nobel Prize in Physiology or Medicine [51]. To emphasize, PD-1 is constitutively expressed in a wide range of myeloid and lymphoid cells, including CD8+ T cells; whereas CTLA-4 is mostly expressed in CD4+/Treg cells [52,53]. These two immune checkpoints represent co-stimulatory molecules that condition the activity and effector function of T cells after the first TCR-induced stimulation [54]. Most cancer cells express Programmed death ligand 1 (PD-L1) and CD80/CD86 on their surface, which interact with PD-1 and CTLA-4, respectively, to induce co-inhibitory signals and T cell exhaustion and anergy [55,56] (Fig. 1A). This dysfunctional state of Tumor-Infiltrating Lymphocytes [TILs] results in decreased production of IL-2, IFN-γ, and TNF-α, and an inability to ensure their cytotoxic function, thereby allowing tumor cells to promote and metastasize [57,58]. Avoiding this state of exhaustion by blocking the interaction between these receptors and their respective ligands is one of the purposes of immunotherapy based on Immune Checkpoints Blocking

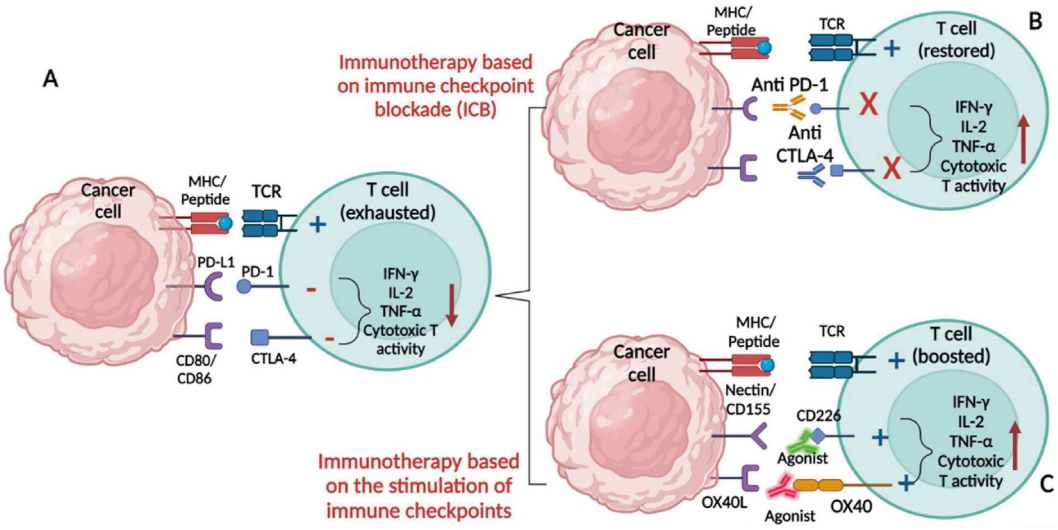

Fig. 1. Concept of cancer immunotherapy targeting immune checkpoints [A] interaction between PD-1 and CTLA-4 on T cells and PD-L1 and CD80/CD86, on cancer cells, results in an exhausted state of T cells [B] Immunotherapy based on immune checkpoint blockade uses antibodies [Anti-PD1/Anti-CTLA-4] to disrupt the interaction and maintain the anti-cancer activity of T cells [C] Immunotherapy based on immune checkpoint stimulation uses antibodies as agonists or recombinant proteins to bind positive immune checkpoints and trigger co-stimulatory pathway.

[ICB] (Fig. 1B). However, some immune checkpoints have the particularity of activating co-stimulatory pathways in effector T cells after coupling with their ligands [59]. For instance, OX40 and CD226 agonists promote the immune cell response by activating CD4+ and CD8+ T cells and increasing their cytotoxic and anti-tumor activity, thereby inducing an appropriate response that contributes to cancer cell death [60,61] (Fig. 1C). However, the biological mechanisms underlying these co-stimulatory pathways need to be reassessed. On one hand, the immune checkpoint blocking strategy is based on a state of T-cell exhaustion that needs to be lifted; stimulation of a positive immune checkpoint can produce a cytokine storm and an excessive response [62]. In the other hand, it appears that the best strategy is to consider immune checkpoint agonists as complements to other traditional therapeutic strategies [61]. Cancer immunotherapy has completely reconfigured the field of clinical research and aroused great hope for patient management.

4. Immunotherapy against toughest cancers and improvement of patient outcomes

Patients with the most severe tumors are usually prone to standard treatment resistance, toxicities, or distant metastases, which sharply reduces the survival rate [63,64]. Under such circumstances, combination therapy and new treatment perspectives appear to be promising strategies for dealing with these events. Immunotherapy based on immune checkpoint inhibition is commonly prescribed for severe and advanced cancer (Table 1). The combination of immunotherapy with chemotherapy/resection surgery or the single use of immune checkpoint blockade in cancer treatment depends to certain clinicopathological characteristics. Estimation of PD-L1 expression by immunohistochemistry has been shown to be one of the most essential prerequisites for the administration of PD-1/PD-L1 immune checkpoint blockade [65,66]. This evaluation of PD-L1 expression allows the calculation of two major scores: the Tumor Proportion Score (TPS) and Combined Positive Score (CPS) [67]. TPS is defined as the percentage of PD-L1+ tumor cells, while CPS refers to the number of PD-L1+ cells [including tumor cells, lymphocytes, and macrophages] [65]. In general, a high percentage of PD-L1+ cells was associated with better immunotherapeutic response (Table 1). Similarly, the percentage of Tumor-Infiltrating Lymphocytes (TILS) is a reliable prognostic marker for immunotherapy delivery [68,69]. Patients undergoing immunotherapy showed significant improvements in overall survival (OS), Disease-Free Survival (DFS), Progression-Free Survival (PFS), and Objective Response Rates. Table 1 summarizes the main immune checkpoint inhibitors frequently used in the treatment of severe and advanced metastatic cancers.

5. Limits of Immunotherapy

Although the use of immunotherapy is crucial and beneficial for patient management, some limitations and side effects of this strategy have been reported.

Table 1. A list of Immune-checkpoints antibodies used in the most aggressive cancers and their benefits.

Cancer Type	Target/Immunotherapy administration	Clinical Trial Phases and Benefits	References
Breast Cancer [BC]	- Anti-PD-1 [Pembrolizumab]/ Single-agent/neoadjuvant	- **PHASE III: Approved by FDA** - Safety and tolerable - Anti-tumor Activity - Improved durability of anti-tumor response compared to standard chemotherapy. - Patients with higher CPS might have longer overall survival with pembrolizumab than with chemotherapy.	[78−80]
	- Anti-PD-L1 [Atezolizumab]/Neo-adjuvant	- Safety and well tolerated - Cytokines production and CD8+ proliferation. - Increased PFS and OS in Patients with high PD-L1 expression compared to those with low PD-L1. PFS [High PD-L1]: 7.5 vs PFS [Low PD-L1]: 5.0 months; HR 0.62, 95% CI 0.49−0.78, $p < 0.001$. OS [High PD-L1]: 25.0 vs OS [Low PD-L1]: 15.5 months. HR 0.62, 95% CI 0.45−0.86]	[81−83]
Breast Cancer [BC]	- Anti-PD-L1 [Avelumab]/Neo-adjuvant	- Safety and tolerable - Modest Antitumor Activity. ORR [all patients] = 3,0%; 5 of 168 patients. ORR [TNBC] = 5,2%; 3 of 58 TNBC]	[84]
	- Anti-PD-L1 [Durvalumab]/Neo-adjuvant	- Long-term antitumour effects. - Safety and tolerable. - Increased survival of TNBC patients with the combination therapy compared to chemotherapy alone. - ORR = 36%; 5 of 14 patients. - DCR = 64%; 9 of 14 patients.	[85,86]
	- Anti- CTLA-4 [Tremelimumab]/Neo-adjuvant	- Safety and tolerable. - Increased anti-tumor activity with stimulation of CD4+ and CD8+ T cells expressing Inducible Costimulator [ICOS]. - 42% of patients with a stable disease [11 of 26 patients]. With a duration ≥12 weeks. - Clinical benefits: Identify patients likely to respond best to CBI based on tumor mutation burden and T cell infiltration.	[87,88]
Melanoma	- Anti-PD-1 [Nivolumab]/Adjuvant	- **PHASE III: Approved by FDA** - Fewer side effects compared to adjuvant ipilimumab. - Significant improvement in the number of patients with 12-month recurrence-free survival, in Nivolumab group. Nivolumab group: 72,3% of patients [12-month recurrence-free survival] - Ipilimumab group: 61,6% of patients [12-month recurrence-free survival]	[89,90]
	- Anti-PD-1 [Pembrolizumab]/Adjuvant	- **PHASE III: Approved by FDA** - Safety and tolerable. - Significant improvement in the rate of patients with 3/5-distant metastasis-free survival and 3,5-years Recurrence-free survival, in both groups. - Pembrolizumab group [PD-L1-positive]: 66,7% of patients [3/5-years distant metastasis-free survival] - Placebo group: 51,6% of patients [3/5-years distant metastasis-free survival] Pembrolizumab group [PD-L1-positive]: 61,4% of patients [3/5-years Recurrence-free survival] - Placebo group: 44,1% of patients [3/5-years Recurrence-free survival]	[91,92]

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Table 1. (continued)

Cancer Type	Target/Immunotherapy administration	Clinical Trial Phases and Benefits	References
Melanoma	- Anti-CTLA-4 [Ipilimumab]/Adjuvant	**- PHASE III: Approved by FDA** - Significant improvement in the number of patients with median 5-years overall survival and 5-years distant metastasis-free survival, in both groups. - Ipilimumab group: 65,4% of patients [5-year overall survival] - Placebo group: 54,4% of patients [5-year overall survival] - Ipilimumab group: 48,3% of patients [distant metastasis−free survival at 5 years] - Placebo group: 38,9% of patients [distant metastasis−free survival at 5 years]	[93,94]
Non-Small Cell Lung Cancer [NSCLC].	- Anti-PD-1 [Pembrolizumab]/Adjuvant	**- PHASE III: Approved by FDA** - Safety and tolerable. - Increased DFS in patients treated with pembrolizumab compared to the placebo group. - DFS Pembrolizumab group: 53,6 months - DFS Placebo group: 42,0 months	[95,96]
	- Anti-PD-1 [Nivolumab]/Neoadjuvant	**- PHASE III: Approved by FDA** - Significant improvement in EFS, DFS and PCR, in both groups. - EFS [Nivolumab + chemotherapy] group: 31,6 months - EFS [chemotherapy] group: 20,8 months - PCR [Nivolumab + chemotherapy] group: 24 months - PCR chemotherapy group: 2,2 months	[97,98]
Non-Small Cell Lung Cancer [NSCLC].	- Anti-PD-L1 [Atezolizumab]/Adjuvant	**- PHASE III: Approved by FDA** - Safety and tolerable. - Increased DFS in patients treated with adjuvant Atezolizumab and PD-L1 positive compared to the chemotherapy group.	[99,100]
Gastric Cancer [GC]	- Anti-PD-1 [Pembrolizumab]/Adjuvant	**- PHASE III: Approved by FDA** - Significant improvement in ORR in patients treated with pembrolizumab compared to the placebo group. - ORR Pembrolizumab group: 74,4% [95% CI, 66.2−81.6] - ORR Placebo group: 51,9% [95% CI, 43.0−60.7] - ORR [Pembrolizumab group]: 10,6 months - ORR placebo group: 9,5 months - The Pembrolizumab + trastuzumab combination improves the response rate by 22,7%.	[101,102]
	- Anti-PD-1 [Nivolumab]/Adjuvant	**- PHASE III: Approved by FDA** - Safety and tolerable. - Significant improvement in OS and PFS in patients treated with nivolumab + chemotherapy compared to those with only chemotherapy. - Median OS [Nivolumab + chemotherapy group]: 14,4 months - Median OS [chemotherapy group]: 11,1 month. - Median PFS [Nivolumab + chemotherapy group]: 7,7 months - Median OS [chemotherapy group]: 6 months.	[103,104]
Renal Cell Carcinoma [RCC]	- Anti-PD-1 +Anti-CTLA-4 Nivolumab + Ipilimumab	**- PHASE III: Approved by FDA** - Safety, raisonnable and tolerable adverse events - Significant improvement in OS, PFS and ORR in patients treated with nivolumab + ipilimumab compared to those with only Sunitinib.	[105,106]

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Table 1. (continued)

Cancer Type	Target/Immunotherapy administration	Clinical Trial Phases and Benefits	References
		- PFS [nivolumab + Ipilimumab group]: 31% of patients [4-years Progression-free survival] - PFS [Sunitinib group]: 17,13% of patients [4-years Progression-free survival]	
	- Anti-PD-L1 [Avelumab]/Adjuvant	**- PHASE III: Approved by FDA** - Significant improvement in PFS and OS, - PD-L1 + patients treated with avelumab + Axitinib had a longer PFS compared than those treated with sunitinib only; [HR 0,62 [95% CI 0.490−0,777]; one-sided P < 0.0001;	[107,108]
Urothelial Bladder cancer [BLCA]	- Anti-PD-1 [Nivolumab]/Adjuvant	**- PHASE III: Approved by FDA** - Increase in DFS in patients treated with the adjuvant Nivolumab and PD-L1 positive compared to the placebo group. - median-DFS [Nivolumab group]: 20,8 months [95% confidence interval [CI], 16.5 to 27.6] - median- DFS [Placebo group]: 10,8 months [95% CI, 8.3 to 13.9] - Nivolumab group [PD-L1 positive]: 74,5% of patients [disease−free survival at 6 months] - Placebo group: 55,7% of patients [disease−free survival at 6 months]	[109,110]
Urothelial Bladder cancer [BLCA]	- Anti-PD-1 [Pembrolizumab]	**- PHASE III: Approved by FDA** - Safety and tolerable. - Significant improvement in PFS and OS, - Pembrolizumab group: 16,7% of patients [Overall survival at 48 months] - Chemotherapy group: 10,1% of patients [Overall survival at 48 months] - Pembrolizumab group: 9,5% of patients [Progression-free survival at 48 months] - Chemotherapy group: 2,7% of patients [Progression-free survival at 48 months]	[111,112]
	- Anti-PD-L1 [Atezolizumab]	**- PHASE III: Approved by FDA** - Significant improvement in PFS and OS, - Median PFS [atezolizumab plus platinum-based chemotherapy group]: 8,2 months [95% CI 6,5−8,3] - Median PFS [placebo plus platinum-based chemotherapy group]: 6,3 months. [95% CI 6,2−7,0] - Median OS [atezolizumab plus platinum-based chemotherapy group]: 16 months [95% CI; 13,9−18,9] - Median OS [placebo plus platinum-based chemotherapy group]: 13,4 months. [95% CI; 12,0−15,2]	[113,114]
Colorectal cancer [CC	- Anti-PD-1 [Pembrolizumab]	**- PHASE III: Approved by FDA** - Significant improvement in PFS in patients treated with pembrolizumab vs chemotherapy group. - Median PFS [pembrolizumab group]: 16,5 months [95% CI 5,4−38,1] - Median PFS [chemotherapy group]: 8,2 months [1,2,2−6,6−10]	[115,116]

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Table 1. (continued)

Cancer Type	Target/Immunotherapy administration	Clinical Trial Phases and Benefits	References
	- Anti-PD-1 + Anti-CTLA-4	**- Phase II** - Safety and tolerable. - ORR [BRAF mutation group]: 76% - ORR [KRAS mutation group]: 80% - Overall population: 73,6% of patients [Progression-free survival at 24 months]	[117,118]

In the first instance, only 15−20% of patients respond favorably to immunotherapy [70]. This low rate is usually due to the limited number of patients eligible for treatment and development of resistance. As previously mentioned, TILs percentage is critical for an objective response [68,69]. It has been shown that patients with an immune-excluded and immune−desert profile do not respond to immune checkpoints inhibitors [71,72]. Moreover, mutations in certain tumor suppressor and interferon pathway genes, such as PTEN, JAK1, and JAK2, can lead to resistance to PD-1 blockade [73,74]. Good results in immunotherapy can only be achieved if the T cells are partially depleted. Unfortunately, hyper-exhausted T cells cannot be perfectly reactivated, resulting in a decrease in the effectiveness of immune checkpoint inhibitors [75,76]. The limitations of immunotherapy can also be attributed to side effects so-called "immune-related side effects", namely Dermatologic toxicities, pulmonary toxicity, hepatitis, neurotoxic effects, myocarditis and death, which are unfortunately detrimental for patients [77].

6. Conclusion

Substantial efforts have been made in the development of 'cancer immunotherapy' for its application as a therapeutic strategy. The recourse to immune checkpoint inhibitors has significantly improved patient outcomes, although in a limited number of patients. With many immune checkpoints being discovered, analyzed, and tested by researchers and clinicians, there is no doubt that promising discoveries are expected and should increase the success rate.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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