Review Article

Immunotherapy and targeted therapy—the new roadmap in cancer treatment

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Abstract: Immunotherapy is the new frontier in cancer medicine. This manuscript summarizes historical aspect of immunotherapy, particularly its pathway to drug approval as the main therapeutic modality used in clinical medicine. We will discuss the role of immunotherapy in treating various types of cancers and how the treatment landscape once dominated by chemotherapy is rapidly changing.

Keywords: Immunotherapy; chimeric antigen receptor T-cells (CAR T-cells); check point inhibitors; cancer treatment

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Introduction

Medicine has witnessed many discoveries in the last century. From the discovery of diphtheria anti-toxin leading to the first Nobel Prize in medicine awarded to Emil von Behring in 1901, to discovery of penicillin by Alexander Fleming, to treatment of HIV, there have been many breakthroughs over the years. This has been amply represented in the distribution of Nobel prizes in medicine and physiology over the years. Every era and every year depicting a breakthrough which has helped humanity in fighting ailments. If twentieth century was the antibiotics era, this century should be dubbed—the immunotherapy era, considering the difference it has already made in improving survival in cancer patients. In this context it would not be wrong to call the year 2018—the year of immunotherapy.

In 2018, the noble prize in medicine was awarded to basic science researcher, James Allison, who is rightfully dubbed as the father of check point inhibitors. Dr. Allison described the checkpoint molecule cytotoxic T lymphocyte associated protein 4 (CTLA-4) and its inhibitory function in the activation of T-cells. In mid 1990s, he showed anti-tumor effect in a series of mouse models by antibody blockade of CTLA-4 (1). This is the critical juncture in history of medicine which shifted the paradigm from attempting to activate the immune system that is vaccinating, to releasing the checkpoints that keep it in negative regulatory mode. This ultimately led to the development of check-point inhibitors and it was in 2011 when the U. S. Food and Drug Administration (FDA) approved ipilimumab. This was the first drug in this class which was noted to improve overall survival in metastatic melanoma (2).

Immunotherapy versus chemotherapy

Systemic therapy for cancer consists of anti-cancer agents administered into the system to damage or destroy cancer cells and hence cancer growth, which can be either molecularly targeted therapy, biological therapy such as immunotherapy or cytotoxic therapy. Cytotoxic therapy, also known as chemotherapy, has been traditionally thought of as the preferred weaponry for all cancers; it is now not a necessary therapeutic foundation for several malignancies. Many people compare giving cytotoxic systemic chemotherapy to “carpet bombing” in modern

warfare where the idea is simple, the goal being to blast off foreign invasion called cancer, regardless of collateral damage. Compare this with check point inhibitors, a type of immunotherapy, very little of cytotoxic side-effects occur. However, check point blockade is associated with a unique spectrum of side effects called immune related adverse events (irAEs) (3). These usually occur due to hyperactivity of the immune system. Grade 1 and 2 irAEs are usually manageable by temporary interruption of treatment and the use of corticosteroids to suppress this hyperdrive of the immune system. Grade 3 and 4 irAEs rarely occurred with immunotherapy, but they are nevertheless managed by high dose of intravenous corticosteroids and other potent immunosuppressive agents like infliximab (4).

Since the first check point inhibitor ipilimumab, newer check point inhibitors are being developed and FDA approved, with much less severity and frequency of irAEs. The field of immunotherapy in cancer care has significantly expanded, with additional monoclonal antibodies differently directed against CTLA-4, programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1). Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-cancer immune response. Results from the CheckMate 026 (5) and CheckMate 370 (6) clinical trials, comparing nivolumab with chemotherapy in patients with metastatic non-small cell lung cancer, showed revolutionary results of improved survival benefit. In 2015, nivolumab was initially FDA-approved for patients with advanced/metastatic non-small cell lung cancer and expanded to many other cancers since.

Expanding impact of immunotherapy on current cancer care

Since the first FDA-approval of ipilimumab treatment in solid malignancies had been significantly impacted by the introduction of immunotherapy particularly with immune checkpoint inhibitors. Immunotherapy was most transformative in the management and treatment of melanoma. Advanced or metastatic melanoma has always been considered the most virulent and resistant of all cancers, with dismal survival rates. The incidence of melanoma is currently on the rise with one-fifth of the diagnosed patients expected to develop metastatic disease (7). Treatment options were limited and included toxic chemotherapy and interferon treatments which had deleterious side-effects, including hypertriglyceridemia, hyperuricemia, hepatotoxicity, flu like symptoms, depressive mood disorder, suicidal thoughts among many others (8). One-year survival rate 25.5% and a 6.2-month median survival duration (9). Ten-year survival rates improved to 22% with the monoclonal antibody directed against CTLA-4, compared to historical control of 10% (10,11). KEYNOTE-001 trial of pembrolizumab in patients with advanced/metastatic melanoma, demonstrated an improved 5-year overall survival rate (OS) to 34% in all patients and 41% in treatment-naive patients (12). The study was one of the first to depict how much we have evolved in treating metastatic melanoma and with more tolerable irAEs. *Table 1* summarizes for various immunotherapies used in clinical practice and the year they were approved for clinical use.

For advanced stage head and neck cancers, cytotoxic chemotherapy is still the first line treatment and prognosis are bad for patients who progress during treatment. Second line therapeutic options were limited, until the advent of introduction of immune checkpoint inhibitors. Nivolumab was the first immunotherapy FDA-approved in head and neck cancers because of the results from CheckMate-141 (13), followed by pembrolizumab FDA-approval for second-line therapy because of the results from KEYNOTE-40 (14).

In most cases, esophageal cancer is a treatable disease, but it is rarely curable in advanced or metastatic disease. Esophageal cancer is not as common in the U.S., but it has limited treatment options and prognosis is poor. Survival rates at 5 years for advanced stages esophageal cancer, is typically 5–20%. Breakthrough in the search for effective second line treatment of patients with advanced esophageal cancers, came from findings of the KEYNOTE-181 trial. Results demonstrated pembrolizumab improve OS in patients with PD-L1 combined positive score (CPS) >10 (15). CPS was developed to evaluate the number of PD-L1 staining cells relative to all viable tumor cells, and it has become a surrogate marker for patients who may benefit from treatment with pembrolizumab. The role of combination pembrolizumab and cytotoxic chemotherapy in esophageal cancers, is currently being studied in the frontline setting in an ongoing phase III trial, KEYNOTE-811 trial (16). In a phase II trial of patients with untreated metastatic gastric, gastroesophageal junctional and esophageal cancers overexpressing HER2NEU, the role of immune checkpoint inhibitor in combination with trastuzumab (monoclonal antibody against HER2NEU) has demonstrated preliminary

Table 1 Selected Immunotherapy drugs in clinical practice

Drug name	Mechanism of action	Clinical uses	Approval year
Ipilulumab	CTLA-4 Antibody	Melanoma metastatic	2011
Nivolumab	Check-point inhibitor	Non-small cell lung cancer metastatic progressive	2015
		Melanoma unresectable or metastatic	2015
		Renal cell cancer advanced previously treated	2015
		Small cell lung cancer, metastatic	2016
		Small cell lung cancer, metastatic in combination with ipilulumab	2016
		Head and neck cancer, squamous cell, recurrent or metastatic	2016
		Urothelial carcinoma, locally advanced or metastatic	2017
		Melanoma unresectable previously untreated, with ipilulumab combination	2017
		Melanoma metastatic with brain metastasis	2018
		Renal cell cancer advanced previously untreated with ipilulumab combination	2018
Pembrolizumab	Anti PD1 monoclonal antibody	Melanoma unresectable or metastatic	2015
		Merkel cell carcinoma, recurrent or metastatic	2016
		Non-small cell lung cancer, metastatic, single agent	2016
		Primary mediastinal large B cell, relapsed or refractory	2017
		Urothelial carcinoma, locally advanced or metastatic	2017
		Non-small cell lung cancer, non-squamous, metastatic in combination	2018
		Non-small cell lung cancer, squamous, metastatic in combinations	2018
		Melanoma Stage III adjuvant	2018
		Cervical cancer recurrent or metastatic	2018
		Gastric cancer recurrent locally advanced or metastatic	2018
		Hepatocellular carcinoma advanced	2018
		Head and neck cancer, squamous cell, recurrent or metastatic	2018
Ibrutinib	Bruton tyrosine kinase inhibitor	Mantle cell lymphoma	2013
		CLL/SLL monotherapy or in combination BR or obinutuzumab	2014
		CLL/SLL with 17p deletion	2014
		Waldenstrom macroglobulinemia, monotherapy or rituximab combination	2015
		Marginal zone lymphoma	2017
Axicabtagene ciloleucel	CAR T-cell immunotherapy	Large B cell lymphoma	2017
Tisagenlecleucel	CAR T-cell immunotherapy	Acute lymphoblastic lymphoma-relapsed or refractory	2017
		Diffuse large B cell relapsed or refractory	2017

promising results, with median progression free survival reaching 11 months (17).

Dramatic improvement in survival benefits with immunotherapy compared to cytotoxic chemotherapy in lung cancers and melanoma, has led to the expanded development of immunotherapy in hematologic malignancies. In recent years, the paradigm for treatment of hematologic malignancies had dramatically changed. Gone are the days when fludarabine based combination chemotherapy was used to treat chronic lymphocytic leukemia (CLL) (18). Imagine the toxicity of chemotherapy compared to the newer treatment options in the form of immunotherapy. Ibrutinib is a small molecular drug that irreversibly binds to an important B cell enzyme, Bruton's tyrosine kinase (BTK). It is essentially the wonder drug being currently used to treat B-cell cancers like CLL, mantle cell lymphoma, and Wald Enstrom's macroglobulinemia, giving patients an effective chemotherapy-free option. Improved survival outcomes in both RESONATE 2 (19) comparing ibrutinib with chlorambucil and iLLUMINATE (20) comparing combination ibrutinib with obinutuzumab (fully humanized CD20 targeted monoclonal antibody) with standard chemoimmunotherapy regimen, validated current use of ibrutinib in front-line setting for patients with CLL. Additionally, the results of the iLLUMINATE trial continued to show progression free survival benefit even in high risk sub-groups (del17p or TP53 mutation, del11q or unmutated IGHV) compared with standard chemoimmunotherapy arm.

In classic Hodgkin lymphoma (cHL), investigators have evaluated the role of check point inhibitors to improve response rates (21-23). Pembrolizumab is another humanized IgG4 isotype antibody that binds to PD-1 located on lymphocytes and blocks the interaction of PD-L1 and PD-1. Results from KEYNOTE-087 (24) demonstrated that treating patients with relapsed refractory classic Hodgkin lymphoma with pembrolizumab, improved overall response rate. Similarly, treatment with combination of nivolumab and brentuximab vedotin, resulted in improved response rates for cHL patients in first relapse (25) and relapsing post-transplant (22). Based on these results and advances anti-PD-1 antibodies have now been FDA-approved for cHL patients with relapse and/or refractory diseases.

Immune checkpoint inhibitors are but one-way modulation of immune system infiltrate and revolutionize cancer care. Another success in immunotherapy is with CAR (chimeric antigen receptor) T-cell therapy. CAR T-cell therapy is considered the most innovative example in personalized cancer medicine. This is a type of treatment in which a patient's own T-cells are changed in the laboratory so they will specifically attack that patient's cancer cells. These T-cells are taken from a patient's blood. Then the gene for a special receptor that binds to a certain protein on the patient's cancer cells is added in the laboratory, to genetically programmed and trained the T-cells to attack cancer cells. The special receptor is called a chimeric antigen receptor. Large numbers of the CAR T-cells are grown in the laboratory and infuse back into the patient. CAR T-cell therapy has been FDA-approved for certain types of lymphoma and leukemia since 2017. Results from ZUMA-1 (26) endorsed the FDA approval of axicabtagene ciloleucel (CD 19 directed CAR T-cell therapy) for patients with relapsed, refractory diffuse large B-cell lymphoma, follicular lymphoma with transformation and high-grade B-cell lymphoma with failure of two prior systemic lines of therapy. Tisagenlecleucel is another CD19-directed CAR T-cell therapy which was FDA-approved and currently being used for treatment of patients with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse (27,28). Complete response rates were 80–90% in this sub-group however the relapse free survival declined to 60 per cent in the 12 months and these are thought to be due to early CAR T-cell loss, also called T-cell exhaustion. Investigators are currently studying the use of immune checkpoint inhibitors in combination with CAR T-cell therapy to determine if the persistence of T-cell can be sustained, hence improving relapsed free survival.

Future directions of immunotherapy and resistance mechanisms

Immunotherapy with immune checkpoint inhibitors has replaced the foundation for many solid malignancies, notably melanoma and lung cancers. The impact is more dramatic in hematologic malignancies. Results from different clinical trials, have demonstrated the shift in treatment paradigm, where immunotherapy (both immune checkpoint inhibitors and CAR T-cell therapy) is completely changing the landscape which was previously occupied by cytotoxic chemotherapy or chemoimmunotherapy in hematologic malignancies. Are we looking at chemotherapy free future in all hematologic cancers? Not likely, as induction chemotherapy is still the standard of care in acute myeloid leukemia and aggressive non-Hodgkin lymphomas

and clinical trials are ongoing to further evaluate the role of immunotherapy-based combination for these patients with aggressive and harder to treat hematologic malignancies. The search goes on for potential immunotherapy targets, resistance mechanisms and how to further enhance their responses. More and more cancer types which were previously considered non-immunogenic with limited role of immunotherapy are now showing signs of change. A very good example being triple negative, her 2 neu positive metastatic breast cancer where ongoing clinical trials show promising results (29).

Pancreatic cancer is another example which has been traditionally known to be resistant to immunotherapy. A detailed understanding of the cancer micro-environment now shows potential for VISTA pathway which can deactivate T-cells and hence suppress immune response leading to theoretical failure of PD-1/PDL1 inhibition. VISTA is expressed on macrophages which play a key role in innate immune response. Studying the milieu in pancreatic cancer shows increased macrophages in the stroma and much higher expression of VISTA pointing towards resistance mechanism for immunotherapy (30,31). Other immune resistance pathway recently discovered is in K-ras mutant lung cancer. The MAPK signaling where expression of a protein called ZEB1 (presence of KRAS mutation is essential), targets the IL17RD protein suppression shutting down the pathway. This protein expression directs epithelial cells to transition to mesenchymal cell lines. This transition is important and noted in development and progression of various tumors (32). This also explains the reason why many tumors become resistant to treatment with the passage of time. This phenomenon called Epithelial to mesenchymal transition has been studied previously in dissemination of cancer cells (33).

Currently there are lot of molecular studies looking into immune resistant pathways and time will tell if we will be able to decipher them effectively to be clinically relevant. A more detailed understanding of the tumor micro-environment, role of small molecule Immuno-oncology, understanding resistance to NK cell immunotherapy against solid tumors, finding molecular markers of resistance, tumor evasion mechanisms and role of combining cytotoxic chemotherapy and its proper sequencing in treatment holds the key to the future.

Conclusions

Immunotherapy is currently becoming the new foundation stone in treatment of various malignancies and more recent clinical guidelines are constantly being updated to incorporate immunotherapy in the mix. This is a field which previously only included cytotoxic chemotherapy. Every researcher irrespective of the organ system is either studying it or trying to incorporate it into clinical trials. The next goal would be to determine sequencing of treatment options and which type of immunotherapy to choose from. CAR T-cells have shown promising results and a leap towards personalized medicine which without any doubts seem to be the future of oncology. Having achieved this status in cancer treatment starting from melanoma then lung cancer and now other cancers, we can only hope for better and better results in all cancer types including hematologic malignancies. New clinical trials are looking to enhance the excellent current clinical response rates achieved by immunotherapy and finding ways to overcome the known and unknown immune resistance pathways. With immunotherapy we are in the right direction and are looking forward to the day when cancer will just be called a chronic disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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