The Libyan International Medical University

Faculty of Basic Medical Science

Immune Regulation Inhibition and Its Usage and Effectiveness In Cancer Therapy

Name: Mohammed Abdulhakim Elgheriyani

Assisted by: Dr. Rashad Shawgi Babiker

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Abstract

Different cancers affect millions of people around the world and is considered one of humanity's greatest challenges, traditionally cancer is tackled by therapeutic methods such as radiation or surgery, chemotherapy as well as transplant. Activating immune cells is a relatively old concept dating back to the early 20th century, whereby they would be able to attack cancer cells via CD8 T cytotoxic cells but the inherent principle of our immune system is the ability to distinguish "self" from "non-self", for example when the T cells recognize a molecule as "non-self" for instance a cancer cell, they attach onto the molecule initiating the immune response, in addition, there are also accelerators and inhibitors, which provide a tight control that prevent excessive activation and autoimmune diseases, Cytotoxic T lymphocyte associated protein 4 (CTLA-4) is one of these brakes that can be manipulated to unleash the full on destruction of tumour cells by CD8 cells, there is also the programmed cell death (PD-1) molecules on T cells that interact with PD-L1 on Antigen presenting cells, by inhibiting these brakes with blocking antibodies, reduction of cancers such as metastatic melanoma can be achieved in addition to small cell carcinoma, renal carcinoma and lymphoma

Introduction

The existence of inhibitory pathways that limit T-cell response has been the target of checkpoint inhibitors, the best example is CTLA-4 which inhibits T-cell activity by binding to B7 and interfering with CD28-B7 costimulation and by binding to CD-80 and CD-86 [(1)] in addition to programmed cell death (PD-1) first discovered in mice, carries a role in inducing "peripheral tolerance" of T cells by binding to PDL-1 in APCs and thereby stopping an immune response[(2)] the mechanism of PD-1 blockade, which is induced by IFN-y , is by sending a negative stimulatory signal or tyrosine

phosphatase to attenuate T cell proliferation, reducing T Cell Receptor signaling by dephosphorylation, which downplays the ability of tumour reactive T cells to carry out a response [3] PD1 has also been found to bind to PDL-2 in lesser amounts [3]It is possible to use Granulocyte monocyte colony stimulating factor tumour vaccines with anti-PD-1, where it is associated with therapeutic benefits[4]IgG4 Antibodies against CTLA-4 by using Ipilimumab has shown long term survival in 20% of patients with stage IV melanoma, and using combination therapy of anti-PD1 or Nivolumab and anti-CTLA4 in melanoma has shown 50% survival benefit[1] Tumours with a low burden of mutation can present as a challenge [1] and so with high levels of PD-1 associated with a better prognosis, mainly because it indicates a stong antitumour response [5] The aim of this study is to explore the mechanisms of Immune checkpoint regulation, how its inhibition improves overall survival and the effects of combination therapy.

Materials and methods

Intravenous I.V doses of Ipilimumab and Nivolumab were given to 53 patients every 3 weeks for up to 4 doses, then Nivolumab was administered alone for every 3 weeks for up to 4 doses (concurrent therapy) and combined therapy followed every 12 weeks for up to 8 doses. In 33 patients previously treated with Ipilimumab, Nivolumab was administered solely every 2 weeks for up to 48 doses (sequenced therapy). [6]

Results

In the study conducted by Wolchock et al an objective response rate of 40% was observed, with a peak of 53% observed when maximum dosage was given (1mg of Nivolumab and 3mg of Ipilimumab per kg) with tumour reduction rate of 80% with concurrent therapy, typical adverse effects such as proliferative T cell activation and neurological manifestations were observed but were familiar to monotherapy and generally reversible. In the sequenced therapy group, an objective response rate of 20% was observed but with less adverse effects being observed (18%) such as autoimmune hypothyroidism and hyperthyroidism, Type 1 Diabetes mellitus and Psoriasis[6]

Discussion

CTLA-4 functions by ligand competition with CD28 and recruitment of inhibitory proteins to downplay T cells intrinsically while it can reverse signaling of CD80 and CD86 on APCs and inhibit cytokine production extrinsically[7] blockade of CTLA-4 does not impose an effect on all T-cells, mainly on CD8 cells, while blockade of PD-1 can restore exhausted CD-4 cells peripherally, increasing antibody, memory cells and CD8 cells[3] As such, PD-1 expression on T cells and B cells was increased in metastatic melanomas and its interaction with PDL-1 mainly on T infiltrating cells (TIL) , tumour cells and APCs, therefore inhibiting T cell signaling[4] It was observed that combined blockade by monoclonal antibodies IgG4 on the PD-1 and PDL-1 interaction can have greater results such as tumour rejection and delay tumour growth [8] at the maximum dose, all 9 patients who showed a response had tumour regression of 80%, with 3 showing a complete response, compared to receiving Ipilimumab or Nivolumab alone, with only 3% of 53 patients showing a response. [6] Clinical benefits of simultaneous blockade is believed to occur due to the activation of CTLA-4 and PD-1 at different times in the same cell population, for example CTLA-4 blockade is effective for peripheral T helper cells and improving memory while inside the tumour microenvironment anti-PD1 is more effective, and that each blockade can enhance a certain population of cells with different immune functions [3] results by Weber et al support the notion that PD-1 has a role in Melanoma tumour microenvironment as the 12 month recurrence free period was higher among Nivolumab receiving patients with stage 3 or 4 resected Melanoma by 70.5% while the Ipilimumab receiving patients had a recurrence free period of 60.8%, adverse effects were less with Nivolumab with 14.4% while Ipilimumab was associated with higher rate of adverse effects with 45.9%. This may be due to CTLA-4 blockade enhancing CD8 cells in systemic circulation [9] Different results obtained between Wolchock et al and Weber et al may be due to sample size, with higher recurrence free rates seen with larger samples and longer duration. Ipilimumab has shown better response targeting metastatic Melanoma compared to the gp-100 vaccine in a study conducted by Hodi et al, indicating it has a better anti-tumour response by immune-induction, but was associated with unwanted auto-immune reactions in 81 patients [10]

namely attacking the digestive tract, skin and endocrine glands, with higher than normal rates of pruritis, hypophysitis, hyperthyroidism, pneumonitis and colitis observed when combining Ipilimumab with Nivolumab than Ipilimumab alone[11] which was concurrent to the results by Wolchock et al suggesting that both drugs act by regulating the immune checkpoint inhibitors and that there is a synergistic response seen in increased autoimmune reactions when taken together, and also that Ipilimumab is associated with more side effects by immune induction systemically. The benefits of applying the two drugs can be seen in longer survival rates in advanced Melanoma patients receiving both, with 58% survival rate with Nivolumab-Ipilimumab regimen, 52% Nivolumab and 34% Ipilimumab[12] similar to the survival rates reported in other studies such as Wolchock, due to mechanism of action affecting different sites at different times during the tumour attack, with Nivolumab having a higher survival rate mainly by downregulating PD-1 in the tumour microenvironment.

Conclusion

Ipilimumab used with Nivolumab has shown to increase survival rates in patients with advanced metastatic Melanoma by acting on different receptors in different sites at different times, Ipilimumab on CTLA-4 found on cytotoxic T cells and Nivolumab against PD-1 inside the tumour microenvironment, mainly on the T infiltrating cells. Despite the associated adverse effects such as autoimmune endocrinopathies, digestive tract diseases and dermal pruritis when using both at the same time, its benefits can outweigh its harms.

Future word

The goal of combination therapy is to increase the time period of patients with advanced metastatic Melanoma or renal-cell carcinoma by manipulating our immune system, while improved results were seen, higher survival rates can be achieved if further research into the cellular mechanisms behind tumour destruction are discovered whereby it would decrease the need of chemotherapy or radiotherapy.

Also discovering ways to effectively inhibit CTLA-4 and PD-1 while causing minimum adverse effects.

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