Combination therapies: the new standard in treating chronic illnesses

By Lan Huang — 2017-02-27

Historically, we have seen combination therapies used to treat illnesses such as malaria, tuberculosis (TB) and AIDS. In all three of these cases, combination therapies, or 'drug cocktails' helped to fight the sickness more effectively than a single agent treatment, writes Lan Huang, chief executive of USA-based BeyondSpring, in an overview of this field.

The trend in oncology has shifted to the use of combination therapy, because it has better efficacy against cancer, will eliminate cells that acquire a single drug resistance and can address multiple steps in the circle of cancer treatment simultaneously.

In the past, combination therapies have been successful, as multiple mechanisms can be employed, and the likelihood of drug-resistant cells forming becomes less likely. According to the US Food and Drug Administration (FDA), a treatment known as highly active antiretroviral therapy (HAART) is a triple-drug cocktail treatment that made AIDS a more manageable disease.

HAART treatment is effective, because the use of multiple drugs disrupts the virus replication at multiple stages. In 1997, the AIDS death rate dropped 47%, much to the credit of HAART treatment. In turn, 1997 was also the same year that AIDS fell out of the top 10 causes of death in the USA for the first time since 1990.

The treatment of the malaria infection has long been employing combination therapies, as well, due to the infection developing resistance to many monotherapy treatments. To counter the resistance, the World Health Organization (WHO) now recommends combinations of antimalarials, each with different modes of action, for the treatment of malaria. The combination treatment greatly delays, or even prevents, the development of resistance to antimalarials.

The WHO also recommends combination therapy for the treatment of TB. Again, with combination treatment, the emergence of resistant strains is greatly delayed or prevented, rendering treatment more effective.

As displayed in the treatment of other illnesses, US pharma giant Merck & Co (NYSE: MRK) notes that combination treatment of cancer generally proves to be more effective than treatment with a single drug. The industry's improved understanding of cancer pathogenesis has led to new treatment options. Of these, targeted agents and cytotoxic therapies also modulate immune responses.

This raises the possibility of effective combinations with immunotherapy. Many targeted therapies affect pathways that are also important to immune development and function. Thus, it is possible that targeted therapies may facilitate immunotherapies' immune responses to tumors. Additionally, immunotherapies may turn the targeted agents' clinical results into long-lasting clinical remission.

According to Nature Reviews Cancer, maturation of dendritic cells, priming T cell activation and differentiation into long-lived memory T cells, are promoted by targeted agents. This implies that combinations of targeted agents with cancer vaccines can boost the results of the vaccines and as effector T cell function.

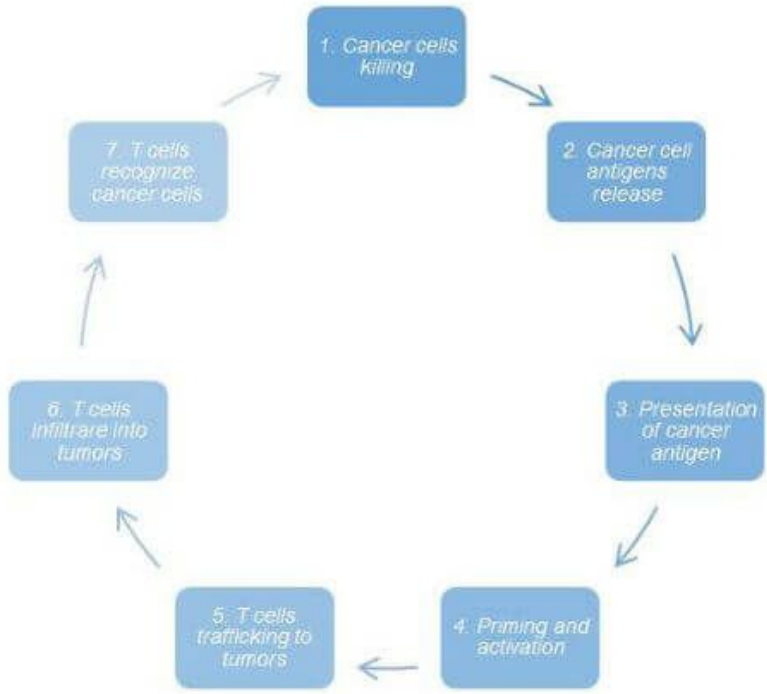

Figure 1

PD-1 antibodies are an example of a targeted therapy. PD-1 antibodies changed the landscape of cancer therapy, but their efficacy against last-stage lung cancer is only 20%. Therefore, the 80% of patients who do not respond to the PD-1 antibody can be treated with the PD-1 antibody and other therapy combinations.

As displayed in Figure 1, PD-1 and PD-L1 agents act only in step 1, cancer cells killing, and step 4, priming and activation in the circle of cancer treatment. PD-1's market success is evidenced by worldwide sales of $1.3 billion for US pharma Bristol-Myers Squibb (NYSE: BMY) for Opdivo (nivolumab) and $1.4 billion for Merck & Co's Keytruda (pembrolizumab). However, PD-1s alone are only effective in 20% of patients. Thus, to increase efficiency, PD-1 manufacturers are interested in

combinations with agents that address other steps in the circle of cancer treatment. For example, B-MS has launched a number of oncology combination trials.

Combination with immunotherapies that produce anti-tumor T cells or increase their effector function may improve outcomes, as targeted agents may reduce tumor-medicated immune-suppression, which increases the function of effector T cells and tumor targets immune destruction. Targeted agents may do this by abrogating tumorigenic inflammation produced and immunosuppressive cell types' inhibiting.

The efficiency of immune-mediated tumor clearance when immune cells are activated in vivo may increase from targeted agents, possibly sensitizing tumor cells to immune-medicated killing by improving the 'distress' ligands (or the expression of death receptors) and reducing pro-survival signals' expression at the same time.

For example, a tumor produces a PD-L1 molecule that interacts with a molecule in the immune system and tricks the immune system. Thus, the immune system does not inform the tumor to self-destruct. 'Checkpoint' immunotherapy drugs interrupt this tumor self-protection process; thus, the tumor can be identified by the immune system for what it is: a defective cell. Manufacturers of checkpoint immunotherapies are keen to demonstrate the improved effectiveness of combining with drugs that are more proactive in killing the tumor cells once the PD-L1 veil has been stripped.

To optimize the effectiveness against cancer and reduce adverse effects, dosing, sequencing and timing of targeted agents will have to be evaluated. Additionally, the cost of combination therapies is generally greater than a monotherapy treatment. While not a perfect solution, combination therapies are a proven method to help manage diseases, particularly cancer, with greater effectiveness.

When 80% of patients with non-small cell lung cancer (NSCLC) failed PD-1 antibody therapy, chemotherapy such as docetaxel is the only choice. However, chemotherapy alone is too toxic. An ideal combination therapy with chemotherapy increases chemotherapy's efficacy and lowers its side effects.

Despite the minor drawbacks of combination therapy, the method still proves to be the most effective in treating a host of illnesses. The trend in oncology has given rise to the study of drugs that employ different mechanisms, which can then be combined to provide a holistic treatment.

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