The next frontier in anti-cancer drugs

openaccessgovernment.org/article/anti-cancer-drugs-treatment-dna/162435

30 June 2023

Dr Anthony J. Berdis, Case Comprehensive Cancer Center discusses the future of cancer treatments and anti-cancer drugs

Being diagnosed with cancer is a horrifying experience for patients and their loved ones. What comes next – discussing treatment strategies – can also strike terror due to the numerous uncertainties associated with the process, procedures that will be used, and possible outcomes. Most cancers are treated using combination therapy in which surgery and/or radiation is first used to remove and eliminate as much cancerous material as possible. This is then followed by several rounds of chemotherapy, an anti-cancer drug designed to eradicate any remaining cancer cells. The goal of this strategy is to achieve remission or at least delay the cancer from returning for as long as possible.

Mechlorethamine was the first FDA-approved anti-cancer drug

Chemotherapy became the standard of care in the 1950s, and the approach was to use a single drug. This monotherapy approach was based, in part, on the accepted clinical concept of using “one drug to treat one disease”. Initial support for this approach was based on early success of Mechlorethamine in treating diffuse large cell B cell lymphoma.

Remarkably, this drug was born on the battlefields of Europe during World War I, and in 1949 was the first FDA-approved anti-cancer drug. At the cellular level, Mechlorethamine is a DNA-damaging agent remarkably similar in chemical composition to sulfur-mustard gases used in trench warfare. Based on the efficacy of Mechlorethamine against lymphoma, other DNA-damaging agents such as cyclophosphamide, BCNU, and cisplatin were subsequently developed and used to treat a wide variety of solid tumors including colon, lung, breast, and pancreatic cancers.

How successful is monotherapy?

Unfortunately, monotherapy is only modestly successful in producing disease-free survival over a 5-year period. This lack of efficacy is caused by several interrelated problems. First,
the axiom of “one drug to treat one disease” does not apply to cancer since most tumors are heterogenous as they consist of different sub-populations of cells that can be sensitive or resistant to a singular anti-cancer agent. Oncologists quickly began to combat this problem by treating patients with mixtures of different chemotherapeutic agents. The goal is to attack different cellular targets responsible for cancer progression and those responsible for drug resistance.

These combinations can also improve the efficacy of each other, generating a synergistic cell-killing effect to eliminate more cancer cells. This synergy means that patients can be treated with lower drug doses to still kill cancer cells without causing significant side effects by damaging normal cells. This strategy has two beneficial effects – first, by extending the life of the patient and secondly, by improving their quality of life.

How do we decide on anti-cancer drug combinations?

The types of drug combinations used clinically depend upon the type and stage of cancer being treated. Since DNA-damaging agents were historically developed first, most combination strategies evolved initially to improve their efficacies and/or combat drug resistance. For example, unresectable pancreatic cancer was originally treated using a combination of the DNA-damaging agent, cisplatin, and gemcitabine, a nucleoside analog.

This combination provides a classic “one, two punch” in which the DNA damaging agent kills cancer cells by inhibiting DNA synthesis while the nucleoside analog reinforces these cell killing effects by also inhibiting DNA synthesis and by blocking the repair of damaged DNA produced by cisplatin. This combination is being replaced by the “FOLFIRINOX regimen” that simultaneously uses three drugs, 5-fluorouracil, a nucleoside analog combined with two DNA damaging agents, irinotecan and oxaliplatin.

Despite improving disease-free survival, combination therapies using DNA-damaging agents still suffer from producing adverse side effects that compromise effective treatments. As a result, there is now a growing shift in combining different classes of agents during treatment. Perhaps the fastest-growing compounds in this area are termed “checkpoint inhibitors”. These are monoclonal antibodies that do not directly kill cancer cells like DNA-damaging agents do but rather improve normal immune function to find and eliminate cancer cells within the body.

Distinguishing foreign cells protects our bodies

One key function of the immune system is to distinguish normal cells from foreign cells such as bacteria, viruses, and cancer cells. This identification process is mediated in part by “checkpoint” proteins present on cells that can activate (or deactivate) a full immune response against foreign cells. For example, PD-1 is a checkpoint protein present on specific immune cells called T cells that functions as an “off switch” to prevent T cells from attacking normal cells. This communication is mediated by the binding of PD-1 to another protein, PD-L1, present on normal cells. The interaction between these complementary partners prevents T cell activation to generate an abnormal autoimmune response.

However, some cancer cells have adapted to express large amounts of PD-L1 on their cell surface. In this case, binding of PD-1 to the excess amount of PD-L1 stops the T cell from attacking the cancer. To block this process, monoclonal antibodies such as Pembrolizumab (Keytruda) and Nivolumab (Opdivo) that by targeting PD-1 to block binding to PD-L1 boosts the immune response against cancer cells. Keytruda was initially

approved in 2014 to treatment numerous malignancies including certain types of skin cancers, breast cancers, and colon cancers. Today, it is often combined with the DNA-damaging agent, carboplatin, and paclitaxel (microtubule inhibitor) to treat various types of lung cancer.

The next frontier in combination chemotherapy

It is clear that tumors do not exist in isolation from other cell types in the body. Indeed, the tumor microenvironment, a diverse ecosystem surrounding the cancer, can directly affect cancer progression and treatment outcomes. Thus, intricacies associated with typical tumor heterogeneity become exponentially more complex due to the co-existence of cancer cells with microorganisms including bacteria, viruses, and even fungus that can influence the activity of chemotherapeutic agents.

A recent study showed that bacteria can metabolize the drug gemcitabine to render it ineffective against pancreatic cancer. Thus, the next frontier in combination chemotherapy will likely combine anti-cancer agents with anti-microbial agents to eliminate bacteria that may adversely affect treatment outcomes. However, this is not likely to be a simple task as it will be necessary to generated selective anti-microbial agents that only kill "bad" bacteria while leaving "good" microbes unaffected.

Please Note: This is a Commercial Profile