Personalized cancer medicines

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Dr. Priya Hays, PhD, CEO and Science Writer at Hays Documentation Specialists, LLC, guides us through the world of personalized cancer medicines

Personalized cancer medicines have emerged with the implementation of precision medicine in oncology, a paradigm shift that had its basis in the Human Genome Project and novel discoveries in cancer biology, along with newfound understandings of the tumor microenvironment.

Novel therapies targeting mutations in solid tumors, such as bevacizumab for colorectal cancer, olaparib for prostate cancer, and abemaciclib for breast cancer, are categorized by their distinct ability for intricately affecting cellular processes that lead to selective cancer cell death.

Immunotherapies have emerged as a class of drugs that are now administered in front-line settings before and after surgical resection. Evolving from Coley's toxins to personalized cancer vaccines, cancer immunotherapies form a broad spectrum of therapies with a formidable armamentarium.

Cancer immunotherapies and more

The emerging role for cancer immunotherapies arose from the classification of tumors as immune- desert regions ("cold tumors"), immune- excluded and immune infiltrated ("hot tumors"). Cold tumors are characterized by the exclusion of cytotoxic CD8+ T cells and natural killer cells and have a high degree of immunosuppressive immune cells such as Tregs. T cells cannot infiltrate the boundaries of a tumor in immune-excluded tumors.

In hot tumors, there is a high degree of responsiveness to therapies such as immune checkpoint inhibitors with active CD8+ T cells and natural killer cells in the tumor microenvironment, as well as suppression of immunosuppressive cell types. [(1)] The latter set of tumors are responsive to immune checkpoint inhibitors.

Immune checkpoint inhibitors are monoclonal antibodies that remove the inhibition on cytotoxic T cells formed by PD-1 and PD-L1 on the surfaces of cancer cells, namely solid tumors. Bispecific antibodies and chimeric antigen T cell receptor therapies have been developed to treat hematologic malignancies like acute lymphoblastic leukemia (ALL) and diffuse large B cell lymphoma (DLBCL), respectively, and the emerging class of therapies, antibody-drug conjugates (ADCs), are being developed for breast cancer.

CAR T cell therapies that have been FDA approved are idecabtagene vicleucel for relapsed/refractory multiple myeloma, and axicabtagene ciloleucel (axi cel) and tisagenlecleucel (tisa cel) for relapsed/ refractory diffuse large B cell lymphoma. Secondary malignancies have been reported as an adverse event in the treatment of CAR T cell therapies, and the U.S. Food and Drug Administration has placed an advisory warning for these therapies.

The mechanistic model underlying the efficacy of bispecific antibodies (BsAbs) are displayed by BiTEs, or bispecific T-cell engagers. Bispecific antibodies have been developed to target tumor cells by redirecting T-cells to distinct antigens on the surface of tumor cells. The antigens, also known as surface epitopes, were first designed with cluster of differentiation markers, specifically CD19 and CD3 epitopes. They comprise a therapeutic class of agents that have remarkable efficacy for hematologic malignances. One of the first FDA-approved agent BiTEs was blinatumomab that has the canonical CD3 and CD19 epitopes.

Antibody-drug conjugates have a similar mechanism to bispecific antibodies in that they engage in immune lysis.

They bind to a receptor on a target cell, and after being internalized through receptor mediated endocytosis, cytotoxic agents are released after being separated from the antibody in lysozyme, where a linker is cleaved, effecting tumor cell lysis. The recent DESTINY clinical trials established the antibody drug conjugate trastuzumab deruxtecan as a new standard of care for the HER2-low molecular subtype for metastatic breast cancer. [(2)]

Oncolytic viral and immunotherapy combination strategies are also being developed. Oncolytic viruses replicate in cancer cells and cause cell lysis. Oncolytic viruses through a “cascade of viral transference between neoplasm and [immune activation]”, lead to antigen release and recognition. Through this proinflammatory environment, the lytic virus leads to “tumor evasion by malignant cells”. Recent studies have shown that these viruses can be harnessed to combine with adoptive cellular therapies, immune checkpoint inhibitors and bispecific antibodies to form combination strategies to form cancer therapies. [(3)]

Artificial intelligence (AI), including machine learning, deep learning, and convolutional neural networks are making sweeping changes in diagnostic pathology and automating the analysis and processing of histopathological samples from cancer patients. AI promises to increase accuracy and analytic validity while decreasing inter- and intra-variability amongst samples.

Renal cell carcinoma or kidney cancer case study

Renal cell carcinoma, or kidney cancer, offers a case study informing how targeted therapies were first developed to treat with safety and efficacy, and cancer immunotherapies were later demonstrated to have superior clinical outcomes. Sunitinib was the standard of care for patients who had just been diagnosed with renal cell

carcinoma. Bevacizumab, a VEFG-A targeted biologic, sunitinib, paxopanib and axitinib (the later three being oral small molecule tyrosine kinase inhibitors) have anti-angiogenic effects and were studied in a series of clinical trials that proved to have robust clinical outcomes and favorable safety profiles and initiated a paradigm shift in the treatment of renal cell carcinoma from cytokines to targeted therapies.

A recent clinical trial later evaluated the combination of the immune checkpoint inhibitors ipilimumab and nivolumab, and demonstrated better clinical efficacy over the targeted therapy sunitinib, with later trials evaluating the immune checkpoint inhibitor pembrolizumab.

With the drug shortages for chemotherapies such as methotrexate, cisplatin and carboplatin, the relevance and importance of personalized cancer medicines may remain greater than ever. Oncologists are facing situations where they cannot provide their patients with life-saving therapies as a result of malfunctioning of drug manufacturing facilities.

However, even within the realm of precision oncology, challenges remain. Immune checkpoint inhibitor approaches are mainly amenable for solid tumors, and CAR T cell therapies and bispecific antibodies target mainly hematologic malignancies; although CAR T- cell therapies are being developed for solid tumors, but these face obstacles.

Also, patients do not always respond to immune checkpoint inhibitors, with a substantial portion being non- responders. Further research is underway to elucidate new approaches for optimizing targeting tumors through personalized cancer medicines.

References

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