

PRECISION MEDICINE AND TARGETED CANCER THERAPY



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The days of science fiction meeting reality are here. Individualized therapy for cancer and chronic disease based on an individual's genomics, lifestyle, and environmental factors are now part of clinical medicine. The Human Genome Project completed in 2003 decoded the entire human genome composed of 3 billion DNA base pairs and identified the exome that contains approximately 23,000 genes. The exome is only 2% of the entire DNA content of the entire genome but is where proteins are encoded. The majority of disease causing mutations occur in the exome.¹

In 2015, the US Precision Medicine Initiative placed cancer research and treatment at the forefront of medical priorities in the country. Precision medicine incorporates the use of genomic information to guide medical decision making.² Targeted therapy is a type of cancer treatment that blocks cancer cell growth by interfering with targeted molecules involved with development of cancer.³

One targeted therapy that has been used in early and late stage breast cancer treatment is Herceptin. Herceptin acts on the receptor site for human epidermal growth factor receptor 2 (Her-2). The Her-2 pathway promotes growth and cell division when it is functioning normally but when the HER-2 protein is overexpressed on cell membranes there is unregulated cell growth and tumor formation. Herceptin blocks the Her-2 receptor function and in turn prevents cancer cell proliferation. Targeted breast cancer drugs may work when conventional chemotherapy does not work and may work in concert with other treatments.⁴ Her-2 chemotherapy medications are similar to other adjuvant chemotherapy agents used for advanced breast cancer. They may cause cardiotoxicity especially if used with anthracycline chemotherapy agents.⁵

Immunotherapy - Check Point Inhibitors

Immunotherapy is actually not a new therapeutic

Executive Summary *Genomic medicine is a powerful tool for clinicians and will influence the way oncologists assess, treat, and follow patients with cancer. The 2003 Human Genome Project decoded the entire human genome opening the gateway for genetic data application to biomedical research and development. The Precision Medicine Initiative 2015 made cancer research a top priority to facilitate the development of precision medicine. Genomic information guiding medical decision making is the impetus behind precision medicine and targeted cancer therapy. Targeted drug therapy uses genomic information about tumor function and growth to target specific cellular proteins to combat malignant cells. Immunotherapy is a form of targeted therapy. It is a method to boost the immune system's ability to detect and destroy cancer cells. So far, the experience with immunotherapy in advanced cancers like melanoma and nonsmall cell cancer of the lung has been encouraging. Checkpoint inhibitors among other immunotherapeutic agents will influence the mortality and morbidity of certain cancers now and in the future.*

modality but has not been particularly beneficial in cancer treatment in the past. However, expanded knowledge about immunology and better understanding about the molecular behavior of cancer cells have led to the creation of new forms of cancer treatment like immunotherapy that can potentially extend and improve the lives of patients living with cancer.

Immunotherapy uses the body's immune system to fight cancer. The immune system is efficient at identifying and destroying tumors even after early malignant transformation. However, the malignant clones are able to evade the immune system's surveillance through a complex process called immunoediting.

One of the ways that cancer avoids the immune system's surveillance is to either reduce the antigenic proteins on the cell surface, or create new surface proteins, neo- antigens, that are difficult to recognize as foreign. In addition, tumors stimulate upregulation of checkpoint inhibitors to promote T cell exhaustion, and produce an immune tolerant environment via cytokine production. Specific cytokines are able to suppress immune responses and promote growth of the tumor.⁶

Given the powerful activity against the immune system by tumor cells, researchers have developed a way to block one method of tumor evasion and allow the immune system to carry out its function. Checkpoint inhibitors are drugs that are monoclonal antibodies. The drugs bind check point receptor sites on T lymphocytes which in turn allows the immune system to process and kill tumor cells.

Pembrolizumab, brand name Keytruda, is a monoclonal antibody that binds to PD-1 (programmed cell death 1) receptor on T- lymphocyte and inhibits the PD-1 pathway that depresses the responsiveness of the immune system. The end result is activation of the immune system with T cell proliferation, increased immune mediators, and tumor destruction. This class of drugs has been shown to be effective against other types of cancers including lung, bladder, head and neck, renal cell, and Hodgkin lymphoma.⁷

Former US president Jimmy Carter is currently receiving Keytruda (pembrolizumab) for metastatic melanoma to the brain. His brain tumor has shrunk and is no longer detectable on imaging studies after use of the medication. Similar responses have been reported in clinical trials with the drug. It is more tolerable than the first checkpoint inhibitor Yervoy (Ipilimumab) that was released 2011. The monthly cost for pembrolizumab at the average dose is around \$14,500. Higher doses which are being used in clinical trials cost up to \$83,000.^{7,8}

Immunotherapy does not work for all people with the same cancers nor does it work for all types of

cancers. Researchers are trying to answer questions about refining patient selection, identifying tumor markers that may be predictive of response to immunotherapy, and determining how tumors develop resistance to drugs.⁷

Tumors with a high number of genetic mutations seem to be susceptible to checkpoint inhibitor activity. The reason for the success with the genetically mutated cells is that they stimulate the immune system. The proteins produced by the abnormal genes in tumor cells are more numerous and more abnormal which stimulate the immune system to react by binding the foreign proteins. Cancers that are hypermutated result from carcinogen exposure like tobacco and ultraviolet light. Melanoma and lymphoma generate a robust immune response and have shown consistent susceptibility to the action of checkpoint inhibitors.^{7,8}

The era of precision medicine is here and it brings tremendous promise for improvement in mortality and morbidity of cancer. The methods for screening and determining treatment options will be very different than what they are now. Genomic information of both the individual and the tumor itself will be critically important in medical decision making. The use of checkpoint inhibitors will continue to expand as researchers delve into the questions that arise with their continued use.

Notes

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About the Author

Lisa Duckett, MD is Vice President and Medical Director for RGA Reinsurance Company. In this role, she provides support for facultative underwriting and underwriter education through presentations and one-on-one interactions. Board certified in insurance medicine, internal medicine and geriatric medicine, Dr. Duckett was in direct patient care for 3 years prior to joining RGA. She began her insurance medicine career in 1998 at ING Reinsurance before moving to Met Life and Genworth Financial as medical director, with responsibility for underwriting education, manual revision, and older age underwriting. Dr. Duckett served as the American Academy for Insurance Medicine (AAIM) planning committee chair for the education program in 2004-2005, and as President of the Midwestern Medical Directors Association (MMDA) in 2004.