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Commentary

The Emperor's New Foes: Twenty-First Century Advances in Cancer Therapy

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The title of my commentary derives from Siddhartha Mukherjee's excellent treatise on cancer entitled "The Emperor of All Maladies" [1]. In his book, Dr. Mukherjee tells us that cancer has been with us for a long time, although it wasn't until the 20th century that somewhat effective therapies were developed. These consisted primarily of surgery, chemotherapy, and radiation, often referred to in a critical manner as 'cut, poison, burn,' because of ineffectiveness, non-specificity, and toxicity issues [2]. The key problem however, for radiation and chemotherapy, is specificity. Although cancer cells are eliminated by these treatments, healthy cells are also destroyed in the process. And surgery simply isn't exacting enough to eliminate all cancer cells from a solid tumor (although it is possible). Since the end of the last century, we have come to understand many of the adaptive mechanisms used by cancer cells to survive and thrive [3]. These include proto-oncogenes and tumor suppressor genes that, when mutated, lead to uncontrolled cellular growth [4]. Tumor-specific proteins have been identified that differentiate these cells from their healthy counterparts. In addition, a better understanding of the metabolism of the cancer cell has unearthed weaknesses heretofore unknown [5]. Along the way, advances in gene editing and stem cell technology have provided powerful tools aiding new therapeutic approaches that are producing a paradigm shift in the war on this dreaded group of diseases. Cancer cells are being revealed as specific targets at the molecular level. I have chosen to briefly describe a few of the more significant therapies that are emerging at this time.

Immunotherapy: The adaptive and innate immune systems defend the body from substances and cells that are foreign (non-self). Besides pathological agents like bacteria and viruses, these systems guard against transplanted tissues from donors other than identical twins, which necessitates the use of immunosuppressive drugs to block organ rejection. Cancer cells, usually possess multiple gene mutations, exhibit altered metabolism, do not communicate with the normal cells, and produce tumor antigen proteins foreign to the host [6,7]. Historically however, cancer cells have rarely been recognized as foreign by the immune system. The reasons for this are complicated, involving in part, the recognition of the host as self. Briefly, the adaptive immune system includes two types of cells: B lymphocytes that produce antibodies used to identify foreign substances (antigens), and T lymphocytes (specifically, killer T cells), responsible for cell-mediated detection and destruction of foreign cells [8]. Normally, T lymphocytes utilize specific surface proteins: the major histocompatibility complex (MHC) and checkpoints; both contribute to determining self from non-self [9,10]. Checkpoints essentially instruct cytolytic (killer T or CD8) cells not to attack normal tissue, otherwise such an action would bring about an autoimmune condition. Cancer cells have developed a means of utilizing these checkpoints so that the immune system does not recognize the cell as foreign. Thus, the cancer cell evades detection and proliferates. The last twenty years have seen advances in the use of monoclonal antibodies as checkpoint inhibitors. These antibodies block the ability of the cancer cell to use checkpoints as a way of evading killer T cell function [10]. Checkpoint inhibitors are a promising path to cancer treatment, but there is still much to understand. While this form of immunotherapy has been effective in melanomas, bladder cancer, and specific lung cancers, other neoplasms (pancreatic cancer, glioblastoma) have been resistant to this approach [11]. Hopefully, as checkpoint pathways (there are more than one) become better understood, more targeted therapies will emerge from this exciting area of cancer research.

Cancer vaccines: Another important facet of immunotherapy is the development of vaccines for specific cancers. Unlike vaccines that prevent illness through memory immunity against a pathological agent, cancer vaccines enhance an immune response to an existing tumor antigen. This includes both tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) [6]. TAAs are self-antigens that are overexpressed in cancer cells (compared with healthy cells) but usually induce immunological tolerance, making them poor immunogenic agents for an effective vaccine. Efforts to improve the immunogenicity of TAAs involve the modification of peptides that break immunological tolerance. Among these approaches is a class of antigens known as heteroclitic peptides that enhance recognition of TAAs [6]. Unlike TAAs, tumor-specific antigens (TSAs) are specific to cancer cells. Even so, they present their own challenges to vaccine development. TSA are highly specific to the individual cancer patient and require extensive resources for the development of specific vaccines [6]. This includes genomic and proteomic screening in a high throughput mode that isn't yet practical on a large scale. Clinical trials are underway for both TAA and TSA vaccines. Both classes of trials present their own challenges. For TAA vaccines, a small number of studies show limited efficacy. One trial on metastatic melanoma in which the vaccine was combined with the cytokine interleukin-2 (IL-2), showed an improved clinical response when compared with IL-2 alone [12]. Multiple phase 1 and phase 2 trials involving various TSA vaccines are being pursued with encouraging results regarding safety and immunogenicity. Targets include glioblastoma, small cell lung carcinoma, melanoma, and BRCA and HER2 -dependent breast cancers [13,14]. To date, there is only one FDA approved cancer vaccine, Sipuleucel-T for prostate cancer (tradename: Provenge [15]). While cancer vaccine development is slow, it remains a very high priority.

Photodynamic therapy: Surgical removal of solid tumors is often plagued by cells that have escaped the procedure. Radiation and/or chemotherapy usually follows surgery to destroy surviving cells with, as noted earlier, attendant toxic effects. A newer post-surgical procedure named photodynamic therapy (PDT) is being deployed as a replacement for these earlier treatment to great effect [16]. PDT involves the use of a chemical called a photosensitizer that is taken up by tumor cells. Uptake of the photosensitizer isn't specific, but it tends to be retained much longer by tumor cells than by healthy cells. Illumination by light of a specific wavelength chemically changes the photosensitizer to produce reactive oxygen species (ROS) that are toxic to cells [17]. Clinically, the procedure involves taking the photosensitizer by injection, topically, or in pill form. After a period of time when retention of the drug is optimally retained in tumor cells (and largely expelled by healthy cells), a laser or other light source is directed to the tumor area. In the case of skin cancers, the light can be applied directly. Internal sites (throat, esophagus, lungs) require an endoscope threaded with a thin fiber optic wire [16]. Clinical studies have shown that PDT has been successful in the treatment of basal cell carcinomas and in early carcinomas of the oral cavity, pharynx and larynx [18]. Other areas that show promise are the treatment of esophageal and bladder cancer [19,20]. To be sure, there are side-effects issues with PDT, including the damage to healthy cells retaining the photosensitizer. PDT can cause burns, swelling and pain in treatment areas [16]. Another limitation of this technology is the range of penetration by the light source which is approximately 1 cm. So basic application of PDT applies to tumors just under the skin membranes lining organs. Nonetheless, as improvements in photosensitizers and light source technology are made, this therapy is in position to replace more toxic and non-specific treatments.

Conclusion

These newer treatments have not eliminated the need for established therapies mentioned earlier. Indeed, immunotherapy is often used in combination with surgery, radiation, and chemo. In the case of former President Jimmy Carter, who was afflicted with malignant melanoma, immunotherapy was accompanied by surgery and radiation [21]. But immunotherapy was the primary component instrumental in eliminating the neoplasm. So eventually these new treatments, due to their specificity and lower toxicity, will supplant the older technologies. Continued improvements in vaccine development (ironically helped by the Covid pandemic) will almost certainly add to the arsenal accumulating against this ancient enemy.

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