Cancer Treatment - Where Are We Heading?

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Cancer is a major killer and one of the biggest challenges faced by humanity. There have been rapid advances in all aspects of cancer treatment including systemic chemotherapy, targeted therapy, surgery, radiation therapy and diagnostics. Cancer consists of a spectrum of diseases with features in common of uncontrolled growth and proliferation of cells, loss of the normal mechanism of programmed cell death and gradually spreading to different healthy organs and tissues of the body. There have been advances in all cancer treatment modalities.

In surgery, treatment has advanced from extensive mutilating surgeries like Halsted's surgery for breast cancer to breast conservation surgery with Sentinel lymph node biopsy and from laparotomies to laparoscopies and robotic surgeries *etc*. There are now stereotactic surgeries in neurosurgery which are more precise and less damaging with optimal tumor resection.

In systemic treatment cytotoxic chemotherapies pioneered cancer treatment for more than six decades starting from anthracyclines and platinum compounds in the sixties to taxanes in the nineties and with more drugs like eribulin and Ixabepilone and more recently Liposomal chemotherapeutic agents *etc*. Targeted therapies are another cornerstone of cancer treatment. Of these the oldest is Tamoxifen the selective estrogen receptor modulator effective in hormone positive early and advanced breast cancer. The next major breakthrough was anti Her2Neu therapy including Herceptin initially and more recently Pertuzumab, Lapatinib and ado-trastuzumab emtansine (T-DM1) which remarkably improved the disease course and survival in patients with Her2Neu positive breast cancer making its survival comparable to Her2Neu negative hormone positive breast cancer [1].

One of the characteristics of cancer is sustained angiogenesis in tumor. Tumor cells stimulate new blood vessel formation which supports growth of tumor, its invasion into surrounding tissues and distant spread. To facilitate this an important factor secreted by tumor cells is VEGF stimulated by hypoxia in the tumor tissue and loss of balance between oncogenes and tumor suppressor genes. This concept was first introduced by Judah Folkman about 40 years ago [2]. VEGF is over expressed by many cancer cells, including carcinomas of the breast, kidney, colon, brain, ovary, cervix, thyroid, bladder, esophagus, and prostate. Bevacizumab being the first FDA approved antiangiogenic agent for colon cancer in 2004 followed by many more including Sunitinib for renal cell carcinoma, Lenalidomide for multiple myeloma, Everolimus for breast and many other tumors [3].

One of the biggest breakthroughs in cancer treatment of the century is immunotherapy which acts by activating our immune system to attack tumor cells. In 2018, James P. Allison and Tasuku Honjo were jointly awarded Nobel Prize in Physiology or Medicine discovering new cancer treatment by inhibition of negative immune regulation. In 1990s, James P. Allison at the University of California, Berkeley, discovered a T-cell protein CTLA-4 which blocked the T cells and subsequent immunity and by blocking the CTLA-4 one could free the T-cell and hence the immune system to attack cancer cells [4]. The first anti CTLA4 antibody is Ipilimumab which has tremendously improved the survival in patients with malignant melanoma. Around that time Tasuku Honjo discovered another similar protein PD-1 on the surface of T-cells with similar function but through a different mechanism [5]. Finally research was carried out involving variety of cancers refractory to several lines of treatment undergoing treatment with these new agents which showed definite response leading to long disease free intervals and in some cases even cure. CTLA-4 and PD-1 blockade, are now referred to as Immune Checkpoint Therapy. Despite being so pivotal in treatment of advanced cancers immune checkpoint therapy has its drawbacks also which are its toxicities which can be even life threatening. They result from a hyperactive immune system which starts targeting the normal tissues as well. Fortunately most of these side effects are usually manageable. Of the two immune checkpoint therapy PD-1 has been found to be more effective and has been approved in lung cancer, renal cancer melanoma, head and neck cancer and breast cancer *etc*. Recently combination of CTLA-4 and PD-1 has been found to be more effective.

Next Generation Sequencing is the most recent advances in cancer treatment. By NGS we can identify

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different somatic/germ-line genetic mutations, including nucleotide substitutions, small insertions and deletions (indels), CNVs, and chromosomal rearrangements in the noncoding regions which facilitate finding targetable mutations providing cancer patients with customized treatment with greater chance of response [6]. Some of the mutations are also predictive of response to a particular treatment *i.e.* chemotherapy. These include Oncotype Dx, micro satellite instability, EGFR and KRAS mutations [6] and so on and so forth. Presently there are many ongoing trials on using NGS of cancer genomes in clinical practice, mainly aiming to identify mutations in tumors that can be targeted by mutation-specific drugs [7].

These innovations and advances in cancer treatment have improved cancer survival tremendously. The limitation is cost of treatment and ease of availability. But with the continuing efforts the day is not far when cancer won't be more than a chronic disease.

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