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Major Breakthroughs in Cancer Therapy

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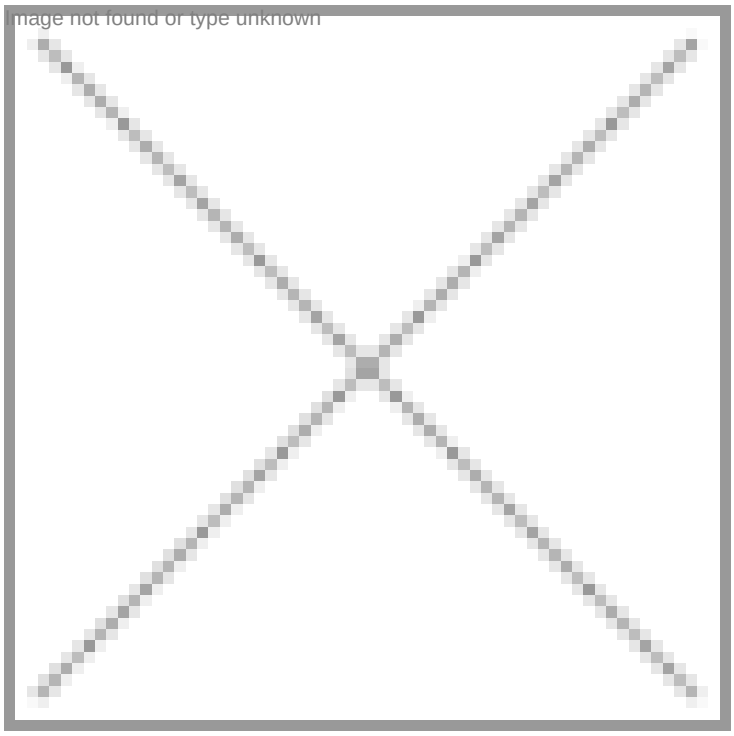

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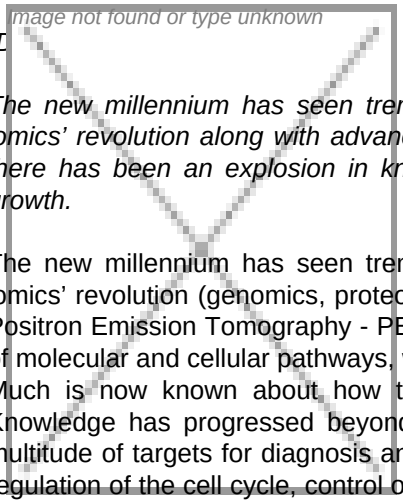

-D officer, Actis Biologics Pvt Ltd.

The new millennium has seen tremendous progress in the diagnosis, prognosis and treatment of cancer. Driven by the 'omics' revolution along with advances in technologies such as cellular imaging, gene knockouts and other analytical tools, there has been an explosion in knowledge of molecular and cellular pathways, which lead to carcinogenesis and tumor growth.

The new millennium has seen tremendous progress in the diagnosis, prognosis and treatment of cancer. Driven by the 'omics' revolution (genomics, proteomics, metabolomics) along with advances in technologies such as cellular imaging (e.g., Positron Emission Tomography - PET), gene knockouts and other analytical tools, there has been an explosion in knowledge of molecular and cellular pathways, which lead to carcinogenesis and tumor growth.

Much is now known about how the cancer cell lapses into uncontrolled cell proliferation compared to a normal cell. Knowledge has progressed beyond the general notion that genetic mutations cause cancer. Biologists have identified a multitude of targets for diagnosis and therapy in a host of different pathways inside the cell. They include checkpoints in the regulation of the cell cycle, control of apoptosis or programmed cell death and prolongation of cell survival. At the tissue level, the role of angiogenesis or blood vessel formation by tumors has been validated as a key mechanism by which tumors survive in the body. Vascular endothelial growth factors (VEGFs) and their receptors have become clinically validated targets for anti-angiogenesis drugs against cancer. Another set of targets is related to epigenetic changes in cancer cells that cause inactivation of factors that regulate DNA expression, such as tumor suppressor genes, repair proteins and microRNAs. Epigenetic markers include DNA methylation/demethylation and histone modifications, which could be

methylation/demethylation or acetylation/deacetylation.
Cancer drug therapy has come a long way from traditional chemotherapeutic approaches using non-selective cytotoxic agents. These were generally small molecules (anthracyclines, platinum compounds, nucleoside analogs, nitrosoureas, anti-folate analogs, nitrogen mustards, etc.) that arrest cell division by either inhibiting DNA replication or disrupting microtubules (vinca alkaloids and taxanes). Since these drugs also attacked normal, non-cancerous cells in the body, they caused severe side effects and morbidities such as hair loss, nausea, oral infections, etc.
It was clear that in order to mitigate the severe toxicities associated with cytotoxic agents administered systemically they had to be targeted selectively into the cancer cell and away from normal cells. Several general approaches have been used towards addressing this challenge, but with limited success. They include the use of prodrugs and liposomal formulations to promote selective accumulation of drugs inside tumor cells compared to normal cells, chemo-sensitizing agents and photo-dynamic (light-activated) agents.
The key discoveries that lead to significant improvement in the survival of breast and prostate cancer patients are the dependence of breast cancer on the female hormone estrogen and the dependence of prostate cancer on the male hormone testosterone. These findings have lead to the development of hormone-based treatments for these two indications that continue to be the cornerstone of early, effective therapy for breast and prostate cancer.
The biotechnology revolution and the development of recombinant DNA therapeutics using cytokines such as interferons and interleukins brought a great deal of promise, but limited success in cancer treatments. Recombinant interferon-alpha-2a (Roferon A, Roche) and interferon-alpha-2b (Intron A, Schering-Plough) have been approved for treatment of several leukemias and other hematological malignancies. Recombinant interleukin-2 (Aldesleukin/Proleukin, Chiron/Novartis) has been approved for melanoma and renal cell carcinoma.
The biggest successes of the era were recombinant G-CSF (Filgrastim/Neupogen - Amgen) and GM-CSF (Sargramostim/Leukine – Immunex/Amgen), both capable of improving white cell count and reversing neutropenia following chemotherapy. The biggest failure of the era was tumor necrosis factor (TNF), which failed to kill any tumor in the clinic and was eventually shown to be one of the key mediators in causing rheumatoid arthritis.

Targeted cancer therapies
Perhaps the most exciting developments in cancer therapy are the three major breakthroughs that have lead to the successful development of more selective, ‘targeted’ therapies that attack tumor cells, while generally sparing normal cells.

- The discovery of tumor-specific antigens and receptors over-expressed in certain tumors.
- The discovery that receptor tyrosine kinase activity plays a central role in tumourigenesis.
- The discovery of monoclonal antibodies and the ability to tailor-make antibodies directed against specific cell surface antigens.

Monoclonal antibodies (MAbs) have revolutionized science, medicine and cancer treatment. Genentech’s Rituxan was the first anti-cancer antibody in the market and several MAb’s have received marketing approval in the US.Dr. Ramani A Aiyer, chief scientific officer, Actis Biologics Pvt Ltd.
Targeted therapies have lived up to the promise of providing novel treatment options for previously intractable cancers such as colorectal, lung and myeloma. They have been a boon to patients who have been given a new lease on life while being spared the morbidities of conventional chemotherapy regimens. Unfortunately, their euphoria may be short-lived, as clinical practice with these marvelous reagents has shown several limitations:
Targeted therapy appears to work best for a limited population of patients who have the ‘correct’ target configuration, e.g., Herceptin for HER2 positive, approximately 30 percent of breast cancer patients and Erbitux for KRAS wild type, about 60 percent of colorectal cancer patients.
The improvement in median overall survival for most cancers is not long, being generally of the order of months over standard of care alone.
It may not be possible to altogether eliminate the use of conventional cytotoxic regimens, as in most cases, the optimal treatment strategy appears to be as combination therapy of the target-specific drug in conjunction with the older regimen.
As cancer cells mutate, targets also develop mutations that make them refractory to treatment, and patients eventually develop resistance to the target-based drug, for e.g., Gleevec resistance due to the T315I mutation in BCR-ABL.

Pharmacogenomics and treatment strategies
There is now a growing body of knowledge on the impact of mutations and genetic polymorphisms on drug responsiveness, which will revolutionize cancer treatment algorithms. Using pharmacogenomics, clinicians can stratify patient populations on the basis of either response or toxicity to certain therapies. This will enable substantial savings in health care costs by fine-tuning therapies towards only those patients who will be responsive, protecting patients who may be at risk for toxic side effects, and using more accurate, individualized dosing regimens.
The US FDA has recommended pharmacogenomic testing of patients before administering two cancer drugs currently in the market. Irinotecan/Camptosar is used for the treatment of metastatic colorectal cancer. Individuals who are homozygous for the UGT1A*28 allele are at increased risk of neutropenia following initiation of Camptosar treatment. It has been

recommended that UGT testing be done on patients to identify those at the highest risk of neutropenia and start them off on a reduced initial dose. Tamoxifen is used to treat breast cancer. Women carrying the CYP2D6 *4/*4 genotype cannot metabolize tamoxifen to its active form, endoxifen. CYP2D6 genotype testing of post-menopausal patients would determine appropriate usage of tamoxifen.

Herceptin, indicated for HER-2 positive breast cancer, was launched along with a companion diagnostic kit for determination of HER2 status in patients before therapy. Clinical studies of patients who are subjected to epidermal growth factor receptor (EGFR) therapies have shown some interesting correlations. In almost all cases and all indications, there is a positive correlation between cutaneous toxicity (skin rashes) and efficacy. More interestingly, mutations in the EGFR kinase domain and the KRAS gene, which is downstream to EGFR, appear to impact the efficacy of therapy.

In colorectal cancer, mutations in the KRAS gene negatively affected responsiveness to cetuximab/Erbitux, whereas patients having the wild type allele in exon 2 (60 percent) showed improved overall survival after Erbitux treatment. In non-small cell lung cancer, mutations in the EGFR kinase domain increased the sensitivity to erlotinib and gefitinib, whereas patients carrying the wild-type alleles were less responsive. Also, mutations in the KRAS gene conferred resistance to the two drugs. Smokers appeared to predominantly harbor KRAS mutations.

The advent of high-throughput DNA microarray and quantitative real-time PCR (qRT-PCR) technologies for gene expression profiling has made possible pharmacogenomic testing using multiple genetic markers and ‘gene signatures’ or profiles comprising hundreds of genes. These tests can be used as diagnostic or prognostic indicators to determine optimum treatment strategies. There are several commercially available gene signature tests for breast cancer and colorectal cancer.

OncotypeDX from Genomic Health is a 21-gene recurrence score assayed by qRT-PCR to predict the risk of breast cancer recurrence and identify those patients with a low risk and therefore may not need adjuvant chemotherapy. DxS Diagnostics/Targeted Molecular Diagnostics has developed a KRAS mutation assay to detect metastatic colorectal cancer patients resistant to EGFR antibody therapies.

Cancer drug discovery in India

Biocon has launched a monoclonal antibody drug called Biomab-EGFR for head and neck cancer in India. Actis Biologics Pvt. Ltd. (ABPL), a start-up biotech, is developing Angiozyme/ABI873, an angiogenesis inhibitor, for colorectal cancer. Angiozyme belongs to a new class of RNA molecules called ribozymes that selectively bind to a mRNA target and degrade it. The target for ABI873 is the receptor VEGFR1, which mediates tumor angiogenesis. The molecule has been in-licensed from Sirna, now acquired by Merck, and has completed one phase-II trial in the US that showed responsiveness in colorectal cancer patients having elevated levels of soluble VEGFR1.

ABPL has filed an Investigational New Drug (IND) with the Drugs Controller General of India (DCGI) to conduct an expanded colorectal cancer trial in India using VEGFR1 as a biomarker to select patients eligible for Angiozyme therapy. Piramal Lifesciences is developing P-276, an inhibitor of cyclin-dependent kinase-4 (CDK-4), targeting the cell cycle, it is currently in phase-II trial for multiple myeloma in the US.

The future

In addition to biologicals such as monoclonal antibodies, the armamentarium of cancer drugs now includes new classes of chemical entities such as anti-sense RNA molecules, cancer vaccines and gene therapy. Many promising therapies are in late stages of clinical development, focusing a wide variety of targets involved in cell proliferation, differentiation and other pathways related to carcinogenesis (cyclins, cyclin dependent kinases, kinesins, Hsp90-Hedgehog pathway, etc.).

While the central challenge of screening and timely detection of cancer at an early stage continues to remain elusive, the significant progress that is being made in pharmacogenomics approaches promises better therapeutic outcomes in the future. Epigenetics and knowledge of the epigenome (patterns of DNA methylation and histone modification) will enable development of new diagnostics tools, better prognosticators and predictors of responsiveness to treatment.