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From the Desk of Director Research

Pharmacogenetics seeks to search for answers to the hereditary basis for inter-individual differences in drug response. This issue focuses on global advances in Pharmacogenetics in Cancer as "Special Feature". DEXA Scan highlighted under "Perspective" is today's established standard for measuring bone mineral density. Autoimmune Haemolytic Anaemia that may be associated with lymphoproliferative diseases, has been dealt with under "In Focus".

The Clinical Trials Registry-India is an on-line register for all clinical trials being conducted in India. A special gratitude to Dr K Satyanarayana, Dr S Srivastva and Dr S Jyoti, IPR Unit, Indian Council of Medical Research, for contributing the "Guest Article" on Registration of Clinical Trials in India.

"Activities of RGCI& RC" include talks on upcoming issues like Personalised Therapy for Cancer, Serrated Polyps and Colorectal Adenocarcinoma & Radiofrequency Ablation. These talks were delivered by eminent clinicians like Dr Shubham Pant, Dr Robert E Petras and Dr Nikhil Patel from USA. Other regular features covered in this issue are: Research and Development; New Technologies; Clinical Trials; Watch-Out; Cancer Control; and Globe Scan.

Our special thanks are to Janssen-Cilag India, Johnson and Johnson Ltd, for supporting this issue of the Cancer News. We also gratefully acknowledge the contributions made by the Clinicians, Scientists and DNB candidates of this Institute. Views and suggestions from readers on the Cancer News are welcome. Happy Deepawali!

Dr (Mrs) Ira Ray

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SPECIAL FEATURE

PHARMACOGENETICS IN CANCER

Introduction

Large inter-individual variation is observed in both the response and toxicity associated with anti-cancer therapy. The etiology of this variation is multifactorial, but is in part due to host genetic variations. Pharmacogenetic studies have successfully identified genetic variants that contribute to this variation in susceptibility to chemotherapy. It is estimated that genetic variability accounts for 20-95% of the variability in therapeutic response and toxic effects. Genomic variation in the human genome is a common phenomenon and approximately one out of a thousand base pairs differs between any two individuals. Most of these variations are single nucleotide polymorphisms (SNPs) and account for >90% of the genetic variation. Insertions and deletions, tandem repeats and microsatellites account for the remaining 10%. The goal of pharmacogenetics is to personalize therapy based on an individual's genotype of medicine. Its implementation into clinical routine diagnostics, including genotype-based recommendations for treatment decision and risk assessment for practitioners, represents a challenge for the future.

Concepts

Basic Concepts: Pharmacogenetic studies can be divided into drug disposition and drug targets:

a) Drug-disposition pharmacogenetics: The disposition of a drug includes its absorption, metabolism, distribution and excretion. If a genetic polymorphism alters the function of a protein involved in the disposition of a drug, the concentration of the parent drug/ its active metabolites at the site of drug action may also be affected.

b) Drug-target pharmacogenetics: Drugs exert their pharmacologic effects by modulating activities of enzymes or receptors. Thus, genetic polymorphisms that change the activity of a drug target may also alter the drug response. If a genetic polymorphism reduces the activity of a drug-target enzyme, the amount of drug required to inhibit the enzyme may be less than the amount required to inhibit the enzyme with normal activity. Also, the drugs that inhibit or antagonize an enzyme or a receptor will produce a greater response at a given dosage in patients whose genetic polymorphisms confer higher activities of the target protein.

The Right Drug for the Right Patient: Same doses of medication cause considerable heterogeneity in efficacy and toxicity across human populations. This heterogeneity can lead to unpredictable life threatening or even lethal adverse effects in small groups of patients. Genetic factors are important determinants for drug efficacy and toxicity. The identification of these genetic factors is the goal of pharmacogenetics. Sequence of the human genome has shown that there is a large extent of genetic variation. Genome sequence could serve as reliable basis for pharmacogenetic research in the years to come.

The major obstacles of cancer chemotherapy are the development of drug resistance and severe side effects. Novel strategies to broaden the narrow therapeutic range by separating the effective dose and toxic dose would be of great benefit for the improvement of cancer chemotherapy. Pharmacogenetics focuses on the prediction of drug efficacy and toxicity based on a patient's or tumor's genetic profile with routinely applicable genetic tests and easily accessible test samples, that is, tumor biopsies or peripheral blood. It holds great promise for the individualization of therapeutic intervention to select the most appropriate medication and to apply the optimal dose for each individual patient according to precise marker-assisted screening test. The hope is to stratify individual patients based on their probability to respond to a particular customized therapy.

Progress in Research

***1. Role of Genetics in Drug Response*:** Heritability analysis determines how much of the variation in phenotype can be attributed to genetic variance. A significant heritable component for a given phenotype provides a strong foundation for follow-up genetic analysis. Heritability can also be estimated in large pedigrees which compares the variations within family pedigrees with those among the population. An approach using cell lines from large pedigrees has been used for several cytotoxic agents, including bleomycin, cisplatin, docetaxel, fluorouracil (5-FU) and daunorubicin.

2. Screening and Identifying Genetic Markers: After confirming the genetic contribution, the next step is to identify the causative genetic markers for the phenotypes of interest, which can be as specific as gene expression, or as broad as overall survival. There are two approaches used to evaluate how genetic variation contributes to human variations in drug response and toxicity: candidate gene and genome-wide.

a) Candidate Gene Approach: Candidate gene approaches focus on one or more candidate genes or pathways and are chosen based on evidence that the gene product is involved in variations in pharmacokinetics or pharmacodynamics and their choice is based on the current knowledge of human pathophysiology, pharmacology and cancer biology. This approach has focused on genes encoding substances involved in the metabolism or transport of anti-cancer agents, as well as drug targets and downstream events leading to apoptosis. These studies are usually conducted using clinically relevant samples (eg, blood, liver, or intestinal tissues or tumor specimens), which represent either drug toxicity or functional sites.

b) Genome-Wide Approach: A genome-wide approach gives equal weight to all genes in the genome and can be used when little is known regarding gene-drug effect in an effort to be unbiased. Genome-wide approaches in pharmacogenetics refer to the global study of genetic variations within the human genome for their effects on drug treatment. Recent advances in genomic technology such as genome scale microarray genotyping platforms, microarray-based comparative genomic hybridization and transcriptional level gene expression platforms along with the development of software to accomplish the analysis of these large data sets, have allowed researchers to perform genome-wide association study between genetics and phenotypes.

3. Validating Genetic Markers: Replication is an important principle in all genetic studies. This is particularly important when a genome-wide approach is used to obtain potential genetic markers. If a genotype-phenotype association is replicated, functional studies are usually performed to gain a better understanding of the nature of the association and identify the causative variant.

4. Clinical Utility Assessment: Once validated, genetic markers can be measured before the initiation of therapy. The information will better inform prescribers as to whether the patient is at an increased risk for non-response and/or developing drug associated toxicities, and can therefore guide their choices of treatment/dose to the individual patient based on the drugs' therapeutic index.

Candidate Genes & Clinical Applications

Candidate genes and their mechanisms can serve as candidates for the analysis of polymorphisms with prognostic power for the efficacy and toxicity of drugs and for survival of cancer patients after chemotherapy.

1. Mechanisms Acting Upstream include transporter proteins for uptake or excretion [i.e., ATP-binding cassette transporters (ABC transport); reduced folate carriers (RFC); nucleoside transporters (hENT, hCNT)] and drug-metabolizing enzymes that activate, inactivate, or detoxify drugs [i.e., *Phase I enzymes:* cytochrome P450 monooxigenases (CYP); *Phase II enzymes:* glutathione S-transferases (GST); UDP-glucoronosyltransferases (UGT); NADH quinone oxidase 1 (NQO1)].

2. Drug Target Interactions include DNA biosynthesis and metabolism [thiopurine S –methyltransferase (TPMT); thymidylate synthase (TS); 5,10-methylenetetrahydrofolate reductase (MTHFR); dihydropyrimidine dehydrogenase (DPYD); cytidine deaminase (CDA)], DNA repair [O^6–methylguanine-DNA methyltransferase (MGMT); x-ray cross complementation group 1 gene (XRCC1); excision-repair cross-complimenting genes ½ (ERCC1/2); human MutS homologue 2 (hMSH2); human homologous recombination 21 gene (hHR21)], mitotic spindle.

3. Mechanisms Downstream include apoptosis cascade [p53; BAX; Fas], chemokines [tumor necrosis factor (TNF); interleukin-6 (IL6); interleukin-10 (IL10)].

P-glycoprotein (ABCBI, MDR1) include anthracycline, anthracendiones, vinca alkaloids, taxanes, epipodophyllotoxins, etc. Nucleoside transporters (hENT, hCNT) mediate the translocation of cytarabine, gemcitabine, fludarabine, cladribine, 5-deoxy-5-fluorouridine, troxacitabine and clofarabine. CYPs can either detoxify anti-cancer drugs like epipodophyllotoxins, paclitaxel, vinca alkaloids and tamoxifen or activate inactive prodrugs like cyclophosphamide. The GST genes are the most extensively studied genes of the phase II enzymes. Several associations have been found between polymorphisms in the various GST genes and cancer treatment response of acute myeloid leukemia, breast cancer, ovarian cancer, colorectal cancer, lung cancer, gastric and pancreatic cancer, multiple myeloma or Hodgkin's lymphoma. Vince alkaloids and taxanes target beta tubulin (constituents of mitotic spindle).

Clinical Applications: Genetic information has been used in the identification of disease risk (e.g. the BRCA1 mutation test to evaluate breast cancer risk), choice of treatment agents (e.g, CYP2D6 in breast cancer treatment; HLA-B* 1502 for carbamazepine); and guiding drug dosing (e.g, CYP2C9 and VKORC1 for

warfarin dosing, UGT1A1 for irinotecan, and TPMT for 6-mercaptopurine and azathioprine). Identifying host genetic variations that contribute to drug efficacy and/or the risk of toxicity will help tailor therapy.

Tamoxifen: Tamoxifen, a selective estrogen receptor modulator, has been successfully used in the treatment and prevention of breast cancer. Recent studies have identified allelic variations in CYP2D6 to be an important determinant of tamoxifen's activity (and toxicity) in relation to hot flashes, recurrences and survival, because CYP2D6 is responsible for the formation of tamoxifen's active metabolite. Tamoxifen is metabolized by CYP2D6 to 4-hydroxy-tamoxifen and endoxifen, which exhibit approximately 100 times greater affinity for the estrogen receptor than the parent drug, tamoxifen. The US FDA recommended a label change for tamoxifen in 2006, including mention of CYP2D6 genotype testing as an option for women before they are prescribed tamoxifen.

Irinotecan: It is commonly used for the treatment of colorectal and lung cancer patients. The prodrug irinotecan is converted in the liver to an active metabolite, SN-38. UDP-glucoronosyltransferase1A1(UGT1A1) conjugates SN-38 to an inactive SN-38 glucuronide, which is excreted into bile and urine. With reduced capacity for glucoronidation, SN-38 can cause life threatening diarrhea. The association between UGT1A1*28 and irinotecan toxicity has been confirmed in multiple studies. Baseline serum bilirubin level has been evaluated in predicting toxicity/ efficacy among patients receiving irinotecan for metastatic colorectal cancer.

6-Mercaptopurine (6MP): 6MP is commonly used for the treatment of acute lymphoblastic leukemia. It is a prodrug that is activated by hypoxanthine guanine phosphoribosyl transferase to 6- thioguanine nucleotides (TGN), which are incorporated into DNA. TPMT inactivates 6MP by S- methylation and thereby prevents the formation of TGN. TPMT activity has been shown to correlate with 6MP toxicity and therapeutic efficacy; the higher the TPMT activity, and therefore less formation of active TGNs; the less 6MP toxicity and the higher risk of disease recurrence after 6MP therapy. Genotyping of TPMT is widely used for dose adjustments to avoid adverse drug reactions.

5-Fluorouracil (5-FU): 5-FU has been widely used in the treatment of solid tumors and remains the backbone of many combination chemotherapy regimens. Despite its clinical benefits, 5-FU is associated with frequent gastrointestinal and hemotologic toxicities, 5-FU undergoes anabolic and catabolic biotransformation. Gene products involved in this transformation include DPYD which breaks down 5-FU and other drug targets (e.g TS and MTHFR). Several of these genes have been shown to affect 5-FU treatment outcomes. DPYD activity is highly variable among patients and its deficiency causes severe life-threatening neurological and gastrointestinal toxicities.

Methotrexate (MTX): It is a folic acid antagonist that is commonly used to treat leukemias, lymphomas and breast cancer. A common genetic polymorphism in MTHFR is predictive of oral mucositis following MTX treatment. Increased DHFR expression causes resistance to MTX.

Perspective

Drug Pathway Profiling: Cancer is caused by multiple genetic factors rather than by single causes. This hampers the reliable prediction of tumor drug response and normal tissue toxicity because the understanding of the precise role of all participating factors is still limited. Genome wide linkage analysis may be a more systemic approach to discover genomic regions likely to harbor genes which determine chemotherapy cytotoxicity.

Clinical Decision Making: The implementation of pharmacogenetics into clinical routine diagnostics is still limited due to the lack of genotype-based recommendations for treatment decisions and risk assessments of practitioners.

Conclusion

Pharmacogenetics has great relevance in cancer therapy because cytotoxic chemotherapeutic agents are often resulting in serious or even fatal toxicities. The majority of current research efforts are still focusing on screening/identifying and validating genetic markers. Pharmacogenetic approaches will help oncologists in the treatment decisions for their patients to maximize benefit and minimize toxicity for each patient, based on the genetic composition of the individual. More insight into the mechanism of action of pharmacogenetic markers, the biological determinates of response to treatment and prognosis in cancer will ultimately lead to individualized cancer treatment based on a combination of genotype and tumor characteristics of a patient.

(Reviewed by Dr Gauri Kapoor, Senior Consultant, Dept of Pediatric Hematology & Oncology)

GUEST ARTICLE

REGISTRATION OF CLINICAL TRIALS IN INDIA

Why Register?

India is increasingly emerging as a preferred destination for the outsourcing of clinical trials with over 80 government and private Indian hospitals engaged in global and local clinical trials. By 2010, the Indian market for global clinical trials would be about US$1-1.5 billion. Several multinational companies have already started simultaneous and stand-alone clinical trials in various therapeutic segments in India. Many Indian pharma companies and Contract Research Organizations are gearing up to meet the challenge.

Clinical trials are expected to be conducted ethically and reported honestly as human volunteers often put themselves at great risk with the belief that such knowledge helps improve health care. However, most data generated are not publicly accessible. Few people, usually a network of investigators, funding agencies, and government regulatory bodies know about a trial from its inception. Most trials become public knowledge only after publication. Some clinical trials conducted by the multinational pharma companies may not be published at all. In the meantime, others may be duplicating the effort or worse, ignoring early warning signs that an intervention is dangerous.

Compounding the problem, there are increasing reports of unethical practices in the conduct of clinical trials both in India and abroad (1). The most recent incidents TGN1412 and Vioxx underscores the need to have a critical relook at the way clinical trials are conducted and reported either underreported or only positive outcomes/results published (1). Not surprisingly, data from over a million controlled trials conducted by pharma companies is unavailable to the public. Pharma industry is extremely reluctant to disclose trial data despite persistent efforts by governments of several countries. Significantly, since a large number of trials, especially early trials (Phase I) tend to be done in the developing world where regulatory systems are rather lax, systems of transparency and accountability need to be strengthened to ensure reliability of data generated, help clinicians interpret research better and minimize duplication of trials that would expose volunteers to avoidable risks. It will also ensure public demand for unbiased evidence on the effectiveness of treatments, and promote public accountability of medical research.

Registration of Trials

Registration of trials is one serious option that should help address this issue. Although several trial registries are available since 1960s, such efforts are fragmented and data scattered (1). Over 500 clinical trial registries are available and the major registries include www.clinicaltrials.gov (NIH register); www.update-software.com/nrronline/Default.htm (Britain's National Research register); http://www.who.int/ictrp/en/ (WHO registry platform); http://www.actr.org.au/actr/handler (Australian Clinical Trial Registry); http://www.clinicalstudyresults.org/ (Industry-sponsored database) *etc.* The trial database of the Pharmaceutical Research and Manufacturers of America (PhRMA) - www.clinicalstudyresults.org launched in the US in 2004 is far from satisfactory from the stand point of transparency and accountability in the reporting of trials.

To address this issue, the International Council of Medical Journal Editors (ICMJE) ,a global forum of editors of medical journals made trial registration mandatory for publication from July 2005 . The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. More recently, the editors of Indian biomedical journals also came out with a similar statement making it mandatory to register trials for consideration of publication from 2010 (2). So,in future any publication in a journal would ensure public access to some critical data.

Where to Register?

The World Health Organization (WHO) in 2006 launched the International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/) for the registration of all interventional trials. An interventional trial is any research study that prospectively assigns subjects to evaluate the effects of one or more interventions (e.g., preventive care, drugs, surgical procedures, behavioural treatments *etc.*) on health-related outcomes. Thus, all early and late trials, trials of marketed or non-marketed products, randomized or non-randomized trials should be registered. All trials will be assigned a number to make it easier to uniquely identify trials. The unique number can help track trials taking place in several sites. However, both

Mandatory Fields for Registration of Clinical Trial in India (www. ctri.in)

i) Primary Register and Trial Identification Number; (ii) Title of Study; (iii) Scientific title of Study; (iv) Secondary IDs, if any; (v) Principal Investigator's Name and Address*; (vi) Contact Person (Scientific Query); (vii) Contact Person (Public Query); (viii) Source/s of Monetary or Material Support; (ix) Primary Sponsor; (x) Secondary Sponsor; (xi) Countries of Recruitment; (xii) Site/s of Study*; (xiii) Name of Ethics Committee and Approval Status*; (xiv) Regulatory Clearance Obtained from DCGI*; (xv) Brief summary*; (xvi) Health Condition/ Problem Studied; (xvii) Study Type; (xviii) Intervention and Comparator Agent; (xix) Key Inclusion /exclusion Criteria; (xx) Method of Generating Randomization Sequence*; (xxi) Method of Allocation/Concealment*; (xxii) Blinding and Masking*; (xxiii) Primary Outcome/s; (xxiv) Secondary Outcome/s; (xxv) Target Sample Size; (xxvi) Phase of Trial*; (xxvi) Date of First Enrolment; (xxvii) Estimated Duration of Trial*; (xxviii) Status of Trial*

* Additional fields sought by the CTRI as in case of WHO.

the WHO and the ICMJE exempt studies designed for purposes other than studying pharmacokinetics or major toxicity (Phase I). This Registry is open to all prospective registrants at no charge, managed by a non-profit organization and should be accessible to public also. The WHO is seeking 20 key trial details to be disclosed at the time of initiation of the trial (3).

The ICTRP is also expected to be a global network of registries providing a set of standards for all registers, a global trials identification system that will confer a unique reference number on every qualified trial providing coordination among the hundreds of clinical trial registries available.

In India, the Indian Council of Medical Research (ICMR) launched the Clinical Trial Registry (India) (CTRI), a national registry of clinical trials at one of its institutes - the National Institute of Medical Statistics (NIMS), New Delhi in July, 2007. With the launch of this registry, India joins the select group of countries like Australia, United Kingdom, the United States and China to have a system that makes researchers conducting clinical trials accountable through public disclosure. The CTRI will register all interventional clinical trials conducted in India and involving Indian patients. However, observational and bioavailability/bioequivalence studies are not currently being registered.

How to Register?

To register a study at www.ctri.in, applicants will have to submit information including the basic data required by the ICTRP and will receive a WHO assigned unique identification number. In addition, CTRI will encourage the investigators to include subsequent protocol amendments and give regular updates on the status of the trial. The person responsible for registering the trial is either the Principal Investigator or the Primary Sponsor, to be decided by an agreement between the parties. Information needed for the registration include Sponsor and Principal Investigator, target sample size, outcomes, phase of trial, method of allocation, concealment, blinding and masking, *etc* (See box above).

The Drug Controller General of India (DCGI) has since made registration of clinical trials being done in India mandatory from June 15, 2009. Any clinical trial initiated after this date will require registration through the CTRI. Registration henceforth becomes a pre-requisite for obtaining DCGI approval for conducting a clinical trial in India. Over 100 trials were registered during June 2009 with overall registration exceeding 350, underscoring the success of the initiative.

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(Dr K Satyanarayana, Dr S Srivastava and Dr S Jyoti, Intellectual Property Rights Unit, Indian Council of Medical Research, New Delhi. Dr K Madhuri, New Delhi)

PERSPECTIVE

DEXA SCAN

Introduction

Dual-energy x-ray absorptiometry (DEXA or DXA) is recognized as the reference method to measure bone mineral density (BMD) with a good precision and reproducibility. The World Health Organization (WHO) has established DEXA as the best densitometric technique for assessing BMD in pos-tmenopausal women and based the definitions of osteopenia (low bone mass) and osteoporosis on its results. DEXA allows accurate diagnosis of osteoporosis, estimation of fracture risk and monitoring of patients undergoing treatment.

Principle

All DEXA systems operate on similar principles. The DEXA machine sends a thin, invisible beam of low-dose x-rays with two distinct energy peaks through the bones being examined. One peak is absorbed mainly by soft tissue and the other by bone. The soft tissue amount can be subtracted from the total and what remains is a patient's BMD. DEXA machines feature special software that compute and display the bone density measurements on a computer monitor in the form of T score and Z score. T score above -1 is considered normal. A score between -1 and -2.5 is classified as osteopenia. A score below -2.5 is defined as osteoporosis.

Techniques for Assessing Bone Mass

A number of technologies can be used to assess mineral density including DEXA and Single-energy x-ray absorptiometry (SXA), quantitative computed tomography (QCT), and radiographic absorptiometry. Quantitative ultrasound uses sound waves to assess properties of bone. Central DEXA devices located in hospitals can measure BMD at the hip or spine but can also be used to measure the total amount of mineral in the whole skeleton or forearm. BMD measured at either site is a strong predictor of hip fracture. Spine BMD tends to change more in response to some medical conditions, such as corticosteroid excess, and to treatments than does BMD of other sites. Peripheral DEXA devices using smaller devices measure bone density in the forearm or heel. Central DEXA devices are more sensitive than peripheral DEXA devices but they are also somewhat more expensive. Peripheral densitometry may help predict the risk of fracture in the spine or hip. These tests are not helpful in following response to treatment, however, and if they indicate that drug therapy is needed, a baseline central DEXA scan should be obtained.

Clinical Uses

DEXA bone densitometry is a simple, quick, accurate and noninvasive procedure for the diagnosis of osteoporosis and is also considered an accurate estimator of fracture risk. Risk factors include recent falls, prolonged immobilization, smoking, alcohol abuse, family history of osteoporotic fractures, estrogen deficiency at an early age (<45 years) and steroid use for more than 3 months.

BMD testing is an appropriate tool in the evaluation of patients who have disease (e. g. hyperthyroidism, hyperparathyroidism, celiac disease, etc.) or use medications that might cause bone loss. In cancer patients, this deficit may be exacerbated by the disease itself or specific cancer therapies, including oophorectomy and aromatase inhibitor (AI) therapy for breast cancer, androgen deprivation therapy (ADT) for prostate cancer (bilateral orchidectomy, luteinizing hormone-releasing hormone [LHRH] agonists), chemotherapy and glucocorticoids for various malignancies. Patients with an advanced stage of one of these cancers is likely to incur fractures or bone metastases.

At present, only 3%–32% of high-risk patients undergo BMD testing. Current Canadian and American breast cancer guidelines recommend that post-menopausal women receiving AIs, and women who have premature ovarian failure related to cancer therapy should have a baseline DEXA BMD test and be monitored closely for the development of osteoporosis. Guidelines for men from the British Columbia Cancer Agency recommend DEXA screening every two years for most patients with prostate cancer on ADT. The WHO has recently released an online survey that combines the DEXA results and a few basic questions and can be used to predict 10-year hip fracture risk for post-menopausal women. This will be coming into more use in the next few years.

Conclusion

DEXA is today's established standard for measuring bone mineral density. It is important to know fundamentals of position, scan analysis and interpretation of DEXA in clinical practice to minimize serious errors and allow proper use of bone densitometry.

(Reviewed by Dr A K Chaturvedi, Medical Director)

RESEARCH & DEVELOPMENT

Cancer Killing Protein

Dr Vivek Rangnekar, Professor of Radiation Medicine at the University of Kentucky's Markey Cancer Centre, discovered the Par-4 gene in 1993 and in 2007, Dr. Rangnekar's team created the world's first breed of super mice by introducing this gene into a mouse embyo. They found that these mice were resistant to all forms of cancer. Now, in another breakthrough, it has been discovered that the Par-4 protein (mass killer of cancer cells) is secreted by most human and rodent cells and can target large numbers of cancer cells by binding to receptors GRP78 on the cell surface. It significantly expands the potential applications of Par-4 to selectively kill the cancer cells. Study found that when the Par-4 molecule binds to its receptor GRP78 on the surface of a tumor cell, it triggers a biological process called apoptosis or 'cell suicide'. This discovery makes Par-4 a very attractive molecule for future research aimed at developing new combination treatment modalities for cancer patients. It is hoped that the next generation of treatments would be even more effective than conventional treatments available today, with fewer and less severe side effects.

(University of Kentucky, Jul 24, 2009)

Genetic Basis for Pancreatic Cancer

According to the scientists, common variants of the gene for ABO blood type are associated with an increased risk of pancreatic cancer. Individuals with the variant that results in blood types A, B or AB were at an increased risk of pancreatic cancer, compared to those with the variant for blood type O. The results provide a genetic basis for those earlier observations. To discover genetic variations that contribute to pancreatic cancer risk, researchers conducted a genome-wide association study. They analysed common variants, called single-nucleotide polymorphisms (SNP), in the genomes of people with or without the disease. They identified several SNPs on the long arm of chromosome 9 that were associated with pancreatic cancer risk and mapped to the ABO gene. Researchers were able to make this important discovery of the potential role of the ABO gene in pancreatic cancer risk, which may lead to improved diagnostic and therapeutic interventions that are needed.

(NCI News, Aug 2, 2009)

New Drug for Leukemia

Children with leukemia are treated with 10 to 12 different chemotherapeutics over a period of two to three years and some of them have long-term and irreversible damage. Tel Aviv University has discovered novel alternative to traumatic chemotherapy. Modern medicine can cure 8 out of 10 cases of childhood leukemia and the new research gives hope and life to the 20% who might not make it as well as those who may experience a relapse. The first researchers to discover a mutation of the JAK 2 protein in patients with Down syndrome, suspected the link of this protein to leukemia. Based on the successful results of this research, a drug already in clinical trial for polycythemia vera may be relevant for acute childhood leukemia while offering a potential hope. JAK 2 inhibitors are not based on chemotherapy and the first experiences with these treatments showed very few side effects. Researchers need to expand these clinical trials to children and adults with high risk leukemia. If initial trials go well, the drug could fast track through approvals and could be available for treating children with leukemia in a few years.

(*Science Daily, Jul 30, 2009)*

Patient Response to Herceptin

Breast cancer patients who are HER-2 positive may be offered Herceptin as part of their treatment. Herceptin has made a major impact in breast cancer treatment but clinical trials have shown that some HER-2 positive breast cancer patients may not respond to it and become resistant to the drug. Breakthrough Breast Cancer scientists have developed a new method of computer modeling to predict a patient's response to Herceptin. Scientists identified that the amount of the protein PTEN in a cell was related to resistance to anti-HER-2 therapy. This model was confirmed in breast cancer cells grown in the laboratory. Scientists examined 122 samples of metastatic breast cancer tumors treated with Herceptin. They used powerful AQUA microscope to see where and how much of a protein is in a cell. They demonstrated that the amount of PTEN, was related to overall survival and patients whose breast cancer tumors had high levels of PTEN survived an average 22 months longer than those with low levels. Researchers have to find ways to translate these findings on predicting a patient's response to Herceptin, from the laboratory into a test that could work in the clinic.

(*Breakthrough Breast Cancer, Jul 30, 2009)*

NEW TECHNOLOGIES

DIAGNOSTICS

Cancer Screening

Researchers at Northeastern University have developed an early-stage, highly accurate cancer screening technology that determines in seconds whether a cell is cancerous, precancerous or normal.The breakthrough technology 'Spectral Cytopathology (SCP)' for spectral diagnosis automatically captures a "fingerprint" of the cell's biochemical composition. It offers the ability to detect abnormal changes in cells even before (structural) changes become apparent. Earlier detection combined with greater accuracy, SCP has a greater than 95% accuracy rate compared to 65 to 70% for current screening methods and would make a significant difference in patient survival rates. It works by capturing a cell's biochemical composition. After a cell sample is obtained through a minimally invasive exfoliation procedure, the cells are probed with infrared light, which interacts with the cell's molecular components and produces a "fingerprint" of each cell's biochemical composition. The data is analyzed by a computer, which reports if the cells are normal, cancerous or precancerous.

(Phys Org Com, Jul 9, 2009)

Decision Dx-GBM Test

St Joseph's Hospital and Medical Center in Phoenix has partnered with Castle Biosciences, Inc to provide the nation's first genomics-based test for patients suffering from glioblastoma multiforme. Decsion Dx-GBM is the most sensitive test available to tell a patient the likelihood of survival with first line therapy. The test results aid patients and physicians with their treatment planning and other decisions. Physicians from across the United States have now begun sending cases to Castle for Decision Dx-GBM testing to be run in St Joseph's DNA Diagnostics Lab. Based on a tumor's expression of a certain set of genes, this molecular diagnostic test can tell a doctor if the tumor is likely to be sensitive or resistant to the standard first-line treatment. If resistant, precious time might be saved by evaluating different treatment plan options. This test is a prime example of translation genomics, closing the loop between the research lab and the clinic.

(St Joseph's Hosp. and Med. Center, Jun 28, 2009)

EQUIPMENTS

Endoscopic Skull Base Surgery

Esthesioneuroblastoma, cancer of the nasal cavity, is a very rare cancer that develops in the upper part of the nasal cavity. While this tumor generally grows slowly, in some cases it progresses rapidly and aggressively. Researchers from Boston University School of Medicine have shown that endoscopic surgery is a valid treatment option for treating esthesioneuroblastoma , in addition to traditional open surgery and nonsurgical treatments. This revolutionary method of surgery performed at Boston Medical Center, one of the few centers in the world, can offer patients endoscopic skull base surgery for these and other skull base tumors.They found that overall, surgery yielded more disease-free outcomes and better survival rates than nonsurgical treatment modalities. Endoscopic surgery produced better survival rates than open surgery group. Although this meta-analysis suggests that the efficacy of endoscopic and endoscopic-assisted surgery is comparable to open surgery for less invasive tumors, further prospective studies are required to establish more definite conclusions, especially for larger tumors.

(Science Daily, Jul 29, 2009)

Vantas Implant

Vantas® (histrelin) is a luteinizing hormone-releasing hormone (LHRH) agonist which inhibits the production of testosterone in the body, therefore slowing the growth of prostate cancer cells. Vantas® represents a milestone in terms of opening up treatment choice for men with prostate cancer that is metastatic, late stage and locally advanced type of the disease.It can offer patients an improved quality of life. The Vantas® implant is a small and flexible device, made from the same materials as soft contact lenses. It is placed under the skin in the upper arm and releases LHRH over a continuous 12 month period, and is an alternative treatment option to other available LHRH therapies which are currently available as treatments given every one or three months. The Vantas® implant is simple and quick to insert and patients can continue to live life, work and travel without the need for more regular injections, although it is still important that they keep to scheduled check-up appointments. Vantas® is also unique in that the implant can be quickly removed in case of hot flushes, impotence or decreased libido.

(Medical News Today, Jul 7, 2009)

NEW DRUGS

Abstral™

Abstral™ is a fast-dissolving tablet for sub-lingual administration of fentanyl, intended for the management of breakthrough cancer pain in patients who are already receiving opioid analgesics. Oxero's partner in Japan has obtained positive phase III results in Japan for KW-2246 (marketed under the brand Abstral™ in Europe), which is approved for the treatment of breakthrough pain in cancer patients. The clinical study results revealed a statistically significant difference between KW-2246 and the placebo and clinical effectiveness was confirmed. In addition, with regard to safety, no unacceptable side effects were found during the clinical study period. The positive phase III results in Japan mark an important step in the international development of Abstral™. Currently, Abstral™ is sold in Sweden, UK and Germany and is ready for launch in France. The product is being prepared for registration in Japan and in the US, the clinical phase III is finalized. License agreements have been signed with Japan, European Union and the US distribution agreement regarding Abstral™ for Russia and the CIS, Bulgaria, Rumania and the Southeast Asian market have also been signed.

(Orexo, Jul 24, 2009)

Alimta for Advanced Lung Cancer

Patients with cancer often receive maintenance therapy to prevent the disease from progression after their tumor has shrunk or the disease has stabilized in response to chemotherapy. The US Food and Drug Administration has approved Alimta (pemetrexed), manufactured by Eli Lilly & Co., the first drug available for maintenance therapy of advanced or metastatic lung cancer. Alimta represents a new approach in the treatment of advanced non-small cell lung cancer (NSCLC). This study demonstrates an advantage in overall survival in certain patients who receive Alimta for maintenance therapy. NSCLC has several subtypes, including squamous cell, large cell, adenocarcinoma and mixed histology cancers. In a 600-patient clinical trial, people with predominantly squamous cell cancer did not benefit from Alimta, but those with other subtypes of NSCLC survived an average 15.5 months following treatment, compared to 10.3 months for patients who received an inactive substance (placebo). Previously, it was used for the treatment of patients with mesothelioma and was later approved for the treatment of patients with NSCLC whose disease worsened on prior chemotherapy drugs and also as an initial therapy for advanced NSCLC.

(US Food and Drug Administration, Jul 7, 2009)

Faster-Acting Prostate Cancer Drug

The most widely used hormone treatments slow cancer cell growth by lowering production of testoster one in the testicles. It takes up to four weeks to reduce testosterone to the required levels. Firmagon® (degarelix), a new fast-acting hormone treatment for advanced prostate cancer offers a rapid impact which is comparable to the immediacy achieved by surgery. Trials have shown that the new drug can reduce levels below 0.5ng/ml within three days in more than 96 percent of patients. This is an important new step for the treatment of advanced hormone-dependent prostate cancer, with Firmagon® offering a new option and hope for many patients. It can also improve the quality of life for patients by avoiding the initial surges in testosterone associated with the most common treatments currently used. It is generally well-tolerated. The most common side effects in clinical trials were hot flushes and weight increase. Firmagon® was launched officially in the UK on June 24, 2009 at the British Association of Urological Surgeons Annual Meeting in Glasgow.

(Medical News Today, Jun 25, 2009)

Veltuzumab

Veltuzumab is a humanized anti-CD20 antibody that differs structurally from Rituxan® (rituximab). It is currently being evaluated in clinical trials for the treatment of non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia. Veltuzumab is safe and effective for patients with relapsed/ refractory B-cell NHL. A recent study included 82 patients with stage III or IV NHL whose disease had progressed following treatment with one or more chemotherapy regimens, including Rituxan. All patients had one or more measurable lesions that were larger than 1.5 cm but smaller than 10 cm. The patients received weekly doses of veltuzumab via intravenous infusion for four consecutive weeks. The results indicated that veltuzumab was well-tolerated, with no grade 3-4 adverse events. Of 55 patients with follicular lymphoma, the overall response rate was 44%, with 27% of patients achieving a complete response. Veltuzumab appeared safe and effective at all tested dose levels.

(Cancer Consultant.com-News, Jul 28, 2009)

CLINICAL TRIALS

Denosumab for Bone Metastases

Bone metastases in several cancer types can lead to serious problems, such as fracture and spinal cord compression. Bisphosphonate drugs such as Zometa® (zoledronic acid), are commonly used to reduce the risk of complications from bone metastases. According to the results of Phase III clinical trial, the investigational drug 'Denosumab' may be more effective than Zometa® in the management of patients with bone metastases from breast cancer. To directly compare the effect of denosumab with Zometa® among breast cancer patients with bone metastases, in a Phase III clinical trial, researchers enrolled more than 2000 patients. Study participants were assigned to receive either denosumab or Zometa® to determine whether the occurrence of bone complications (skeletal related events) differed between the two study groups. Patients treated with denosumab remained free of bone complications longer than patients treated with Zometa®.

(Cancer Consultants.com-News, Jul 8, 2009)

Sipuleucel-T in Prostate Cancer

Sipuleucel-T is an autologous active cellular immunotherapy that stimulates an immune response against advanced prostate cancer (CaP). In two identically designed randomized phase III clinical trials D 9901 and 9902A, all participants had CaP with evidence of metastases, castrate levels of serum testosterone and at least 3 months survival expectancy. They all had evidence of disease progression either radiographically or by PSA progression. Participants were randomized to either Sipuleucel-T or placebo. In the combined analysis, baseline characteristics were comparable between the two treatment arms. A PSA response rate of 4.8% was observed in the Sipuleucel-T group compared to 0% in the placebo group. The Sipuleucel-T patients had a 21% reduction in the risk of disease progression and a 33% reduction in the death compared with men randomized to placebo. The percentage of patients alive at 36 months was 33% for Sipuleucel-T and 15% for placebo. Cumulative CD 54 upregulation, an antigen-presenting cells during manufacture of Sipuleucel-T, was strongly correlated with overall survival in the Sipuleucel-T arm.

(Uro Today.com, Aug 10, 2009)

Tarceva® for Lung Cancer

Tarceva® (erlotinib) is a targeted therapy that works by blocking epidermal growth factor receptor pathway. It has been approved for treatment of non-small cell lung cancer (NSCLC) after failure of initial chemotherapy. In a phase III clinical trial known as SATURN, Roche researchers have evaluated the safety and effectiveness of Tarceva® maintenance therapy, which refers to treatment that is given after initial treatment but before cancer progression. It is a relatively new approach to lung cancer treatment. The study enrolled more than 880 patients with advanced NSCLC that had not progressed following initial, platinum-based chemotherapy. Half the patients received Tarceva® maintenance therapy and half received a placebo. Previous results indicated that Tarceva® improved progression-free survival. Current analysis focused on overall survival, and found that patients treated with Tarceva® live longer than patients treated with placebo, suggesting that maintenance therapy improves both progression-free and overall survival among patients with advanced NSCLC.

(Roche Media Release, Jul 13, 2009)

XELOX More Effective for Colon Cancer

An international phase III study has demonstrated that XELOX (Oral Xeloda® plus oxaliplatin) is more effective than standard chemotherapy regimen in adjuvant (Dukes'C) colon cancer and may offer a new option which could help prevent colon cancer from returning. The NO16968 trial, also known as XELOXA (phase III XELOX vs 5-FU/LV in adjuvant colon cancer), is an open-label, randomized study of XELOX versus 5-fluorouracil/leucovorin (5-FU/LV) as adjuvant therapy for patients with stage III colon cancer who had undergone surgery and had no previous chemotherapy. The study was conducted at 240 study sites across 29 countries. The data showed that those who participated in the study and took XELOX immediately after surgery lived longer without their cancer being detectable than those who took intravenous 5-FU/LV. No new adverse events related to Xeloda® were observed in the study. Xeloda® is FDA-approved oral chemotherapy for metastatic breast cancer, Dukes'C colon cancer and metastatic colorectal cancer. Now, there is evidence that XELOX is superior to infused 5-FU/LV in increasing the time people with stage III colon lived without their cancer returning when given immediately after surgery.

(Genentech, Jul 20, 2009)

WATCH-OUT

Cancer-Specific Promoters

The present invention by Huge Mien-Chie et al provides a long-felt need in the art to provide breast and ovarian tissue-specific expression of gene sequences to facilitate targeted gene therapy. The Patent Publication No. is US 2009192101 (A1), entitled "Cancer-Specific Promoters" published on July 30, 2009. It regards cancer-specific control sequences that direct expression of a polynucleotide encoding a therapeutic gene product for treatment of cancer. Specifically, the invention encompasses breast cancer-specific and ovarian cancer-specific control sequences. Two breast cancer-specific sequences utilize specific regions of fatty acid synthase and claudin 4 promoters, particularly in combination with a two-step transcription amplification sequence and/or a post-transcriptional control sequence. Two ovarian cancer-specific sequences utilize specific regions of hTERT and survivin promoters, particularly in combination with a two-step transcription amplification sequence and/or a post-transcriptional control sequence. In more particular embodiments, these polynucleotides are administered in combination with liposomes.

(European Patent Office, Aug 8, 2009)

Directed Complementation Technology

The US Patent and Trademark Office has granted US Patent No. 7,556,796 to AVEO Pharmaceutical, Inc. for its Directed Complementation Technology, which greatly enhances the speed at which AVEO can develop its proprietary *in vivo* mouse models of cancer and further differentiates the approach to cancer drug development. The term "directed complementation" reflects that in this technique, an inducible recombinant oncogene originally responsible for a growth of tumor is switched off and then functionally complimented by a recombinant oncogene of choice. AVEO has already used this technology to produce model tumors driven by more than 50 different oncogenes. This approach enables to create tumors whose *in vivo* proliferation and survival are driven by the target gene of interest, providing an invaluable tool to assess the *in vivo* activity of a broad range of candidate targeted therapies and the relevant cancer biomarkers.

(Buisness Wire, Jul 9, 2009)

MAGE Positive Cancer

The inventors Brichard Vincent and Lehmann Frederic Eugene have been assigned patent No. US 2009186049 (A1) entitled "Method of Treating MAGE Positive Cancer" published on July 23, 2009. MAGE antigens are encoded by the family of Melanoma-associated antigen genes (MAGE). MAGE genes are predominately expressed on melanoma cells (including malignant melanoma) and some other cancers.

The present invention relates to methods for treating a range of MAGE-expressing cancers, including but not limited to melanoma; breast cancer; liver cancer; bladder cancer including transitional cell carcinoma; lung cancer including non-small cell lung cancer (NSCLC); head & neck cancer including squamous cell carcinoma (SCC) and oesophagus carcinoma; colon carcinoma; seminoma; and multiple myeloma. MAGE-3 is expressed in 69% of melanomas, 44% of NSCLC, 48% of head & neck SCC, 34% of bladder transitional cell carcinoma, 57% of oesophagus carcinoma, 32% of colon cancers and 24% of breast cancers. This invention relates to methods for treating MAGE-expressing cancers in the adjuvant setting and in active disease, and to the use of a vaccine in the treatment of patients suffering from MAGE-expressing cancers in these settings.

(esp@cenet.com, Aug 7, 2009)

Treatment and Prophylaxis of Cancer

The inventors Gross Richard A and Bluth Martin H, both of USA, have been assigned patent [No. US 2009186835 (A1)], entitled, "Treatment and Prophylaxis of Cancer," published on July 23, 2009. This invention provides a method and composition for prophylaxis or treatment of humans or animals for cancer using a mixture of sophorolipids, members of glycolipid family. Glycolipids have varied biological activities and potential for therapeutic uses. Method demonstrated sophorolipid-mediated cytotoxic responses to cancer cell lines. These anticancer responses were dose and derivative-dependent and likely killed cancer cells by necrosis. These agents are specific to cancer cells in that they do not affect normal cells. Therefore, sophorolipids represent a unique and novel class of drugs, which may be an important promising therapy against cancer. Analysis of dose-dependent responses demonstrated that sophorolipid derivatives differed in their ability to kill cancer cells.

(European Patent Office, Aug 8, 2009)

CANCER CONTROL

Global Access to Cervarix

The World Health Organization (WHO) has approved Glaxo-SmithKline's (GSK) Cervarix cervical cancer vaccine. The approval would help speed access to Cervarix globally. WHO had previously approved Merck and Co's Gardasil. More than 80% of the estimated 280,000 cervical cancer deaths a year occur in developing countries. Women in developing countries are more vulnerable to cervical cancer and the global health association GAVI, formerly known as the Global Alliance for Vaccines and Immunization, is very eager to offer women in developing countries these vaccines. GAVI includes UN agencies, the World Bank and the Bill and Melinda Gates Foundation and is a major buyer of vaccines for the developing world. Vaccine's price is essential to making it available to poor countries and GAVI is in talks with drug makers Merck & Co and GSK to sell their vaccines to donor agencies at a cheaper price.

(USA Today, Jul 9, 2009)

Oral Spray for Mucositis

Oral mucositis is one of the most common and serious complications of radiation therapy for head and neck cancer. It is painful, interferes with eating and drinking and can also lead to severe infection that may require a reduction/ delay in cancer treatment. A study conducted by researchers in Korea suggests that an epidermal growth factor (EGF) oral spray may help reduce oral mucositis in patients undergoing radiation therapy for head and neck cancer. EGF is a protein that plays several important roles in the body, including wound healing and tissue growth. Patients treated with radiation therapy with or without chemotherapy were assigned to receive one of three doses of the EGF oral spray or a placebo. The spray was used twice a day through week five of radiation therapy. Results showed that response rate among patients in the placebo group was 37% and in the EGF spray groups was 57.7% at the lowest dose, 64% at the median dose and 59.1% at the highest dose. Severe (grade 3 or worse) oral mucositis developed in 33.3% of the patients in the placebo group, but in less than 20% of patients in the EGF spray group. The spray is undergoing additional study.

(Cancer Consultants.com-News, Jul 21, 2009)

Physical Exercise in Cancer Control

According to a study conducted in the universities of Kuopio and Oulu in Finland, physical inactivity during a person's life time could be a key factor in the person developing cancer. People who are more active and exercise harder are less likely to develop cancer and die. A higher use of oxygen consumption during physical activity is linked to a reduction in the level of illness in a person and their likelihood of dying from cancer. The intensity of physical activity was measured in metabolic unit (MET or metabolic equivalents of oxygen consumption). Walking was measured as having an average intensity of 4.2 MET, jogging10.1 MET, swimming 5.4 MET, yard work/gardening/farming 4.3 MET and bicycling to work 5.1 MET. They found that average intensity of men's physical activity was 4.5 MET and the average duration of activity was 462 minutes per week. An increase of 1.2 metabolic units was related to a decrease in cancer mortality mainly due to lung and gastrointestinal cancers. Men who exercised moderate to high intensity level for at least 30 minutes a day were half as likely to get cancer as those who did not. Researchers concluded that intensity of leisure-time physical activity should be at least moderate so that beneficial effect of physical activity for reducing overall cancer mortality can be achieved.

(Br J Sports Med, Jul 28, 2009)

Vegetarian Diets Help Control Diseases

A position paper on vegetarian diets released by American Dietetic Association indicates that vegetarian diets, if well planned, can help prevent and treat chronic diseases, including heart disease, cancer, obesity and diabetes. Vegetarian diets are often associated with health advantages, such as lower blood cholesterol levels, lower risk of heart disease, lower blood pressure levels and lower risk of hypertension and type 2 diabetes. Vegetarians tend to have a lower body mass index and lower overall cancer rates. Vegetarian diets are lower in saturated fat and cholesterol and have higher levels of dietary fibre, magnesium and potassium, vitamin C and E, folate, carotenoids, flavonoids and other phytochemicals. These diets are appropriate for all stages of the life cycle. Appropriately planned vegetarian diets are healthful, nutritionally adequate and may provide health benefits in the prevention and treatment of certain diseases.

(Science Daily, Jul 3, 2009)

GLOBE SCAN

Sunbeds and UV: Carcinogenic to Humans

The International Agency for Research on Cancer (IARC), the World Health Organization agency that developed the most widely used system for classifying carcinogens, has classified sunbeds and exposure to ultraviolet (UV) radiation (including sun exposure) as having highest cancer risk to humans" (Group I), whereas earlier, they were classed as "probably carcinogenic to humans" (Group 2A). IARC's decision was based on a comprehensive review of current research that found that starting to use sunbeds before the age of 30 increased a person's risk of developing the deadliest form of skin cancer by 75 percent. Most skin cancers are caused by too much exposure to UV rays. Much of this exposure comes from the sun, but it also comes from manmade UV emitting tanning devices, such as sunbeds and sunlamps. The IARC has also moved all types of ionizing radiation into Group I, which include radon gas, plutonium and its decay products, radium and its decay products, phosphorus-32 and its decay products, radio iodine.

(France: The Lancet Oncology, Aug 2009)

NCDs the Next Health Tsunami

The World Health Organization has projected that globally non-communicable diseases (NCD) deaths will increase by 17% over the next 10 years. The emerging epidemic of NCDs is threatening to overwhelm healthcare systems worldwide unless action is taken. The International Diabetes Federation (IDF), the International Union Against Cancer (UICC), and the World Heart Federation (WHF) have called up on the UN's Economic and Social Council (ECOSOC) in Geneva to avert this fastest growing threat to global health. The global call demanded five essential actions: (i) Call for an 'MDG plus' containing NCD progress indicators in the 2010 Millennium Development Goals (MDGs) review; (ii) Support the availability of essential medicines for people living with NCDs; (iii) Support a UN General Assembly special sessions on NCDs; (iv) Support immediate and substantial increase of funding for NCDs; and (v) Integration of NCD prevention into national health systems and the global development agenda.

(Switzerland: Medical News Today, Jul 9, 2009)

Oncology Information eXchange

The National Cancer Research Institute (NCRI), a UK-wide partnership between the government, charity and industry, has launched a free online cancer research portal ONIX (Oncology Information exchang), aimed at clinical cancer researchers, clinicians, bioinformaticians and health informaticians from both public and private sectors. It provides resources and information on all aspects of global cancer research from genomics to clinical trials. It would provide a unique research environment online and enable scientists and clinicians to search through and access international research data held online to improve the flow of cancer research information between individuals, institutions and organizations. The portal uses powerful search technology which significantly reduces the time to find cancer-related data and information across the spectrum of research. It reduces duplication of research effort across the globe and makes it easier for researchers to collaborate on similar studies. It would speed up the development of new therapies and could improve prognosis and diagnosis. ONIX represents a major advance for cancer research in the UK and its service would be further developed until at least March2010.

(UK: Cancer Research UK, Jul 19, 2009)

FDA's Warning on Electronic Cigarettes

According to the laboratory analysis by the US Food and Drug Administration, electronic cigarettes, or e-cigarettes, contain carcinogens and toxic chemicals. Diethylene glycol, a toxic chemical used in antifreeze, was detected in one sample and a number of carcinogens, including nitrosamines, were detected in other samples. E-cigarettes are often sold as a way to quit smoking or to get nicotine in places where smoking isn't allowed, but are not currently regulated by the FDA. The FDA is concerned about the safety of these products and how these are marketed to the public. Of special concern to parents is the fact that e-cigarettes are sold without any legal age restrictions and their different flavors may appeal to youths. These cigarettes also lack any health warnings like those used with conventional cigarettes and FDA-approved nicotine replacement products. The agency believes that electronic cigarettes should be classified as a "combination drug-device product" liable to be regulated under the Federal Food, Drug and Cosmetic Act.

(US: NCI Bulletin, Jul 28, 2009)

ACTIVITIES OF RGCI&RC

PERSONALISED CANCER THERAPY

Dr Shubham Pant, Assistant Professor of Medicine & Director of Clinical Trials, Section of Hematalogy-Oncology, University of Oklahoma Health Sciences Centre, Oklahoma City, USA, visited Rajiv Gandhi Cancer Institute & Research Centre on August 17, 2009 to deliver a lecture on "Personalized Therapy for Cancer: Recent Developments and Future Challenges". The lecture was attended by Medical Director, Director (Research), Consultants, DNB Students & Research Officers of the Institute.

Dr A K Chaturvedi, Medical Director, briefed on the importance of person to person variations in response to cancer therapy and how oncologists must plan the therapy accordingly. He welcomed and invited Dr Pant to deliver the lecture. Dr Pant began the talk by explaining the targeted therapy included drugs used to block growth and spread of cancer interfering with specific molecules involved in carcinogenesis and tumor growth.

The first study he mentioned was therapy of metastatic Gastro Intestinal Stromal Tumor (GIST). GISTs are a type of leiomyosarcomas which do not express muscle or schwann cell markers but instead express c-kit and hematopoetic progenitor cell markers like CD34. Therefore, Imatinib, a tyrosine kinase inhibitor used for chronic myeloid leukemia was tried in patients with GIST. The trial results proved that overall survival was significantly improved by imatinib therapy and it is now the mainstay of GIST treatment.

The second study he touched upon was about targeted therapy in lung cancer. Conclusions of the trials were that patients who had somatic mutations of tyrosine kinase domain on epidermal growth factor receptor gene on chromosome 7, responded better to gefitinib therapy than those who didn't possess mutations; and also that pharmacokinetics of erlotinib at mean tolerated dose differed in smokers and non- smokers. Smoking induced CYP1A1/1A2 which hastened the metabolism of erlotinib and therefore, required higher dosage of erlotinib.

Trials were also conducted in colorectal cancer patients assessing the response of cetuximab in patients with mutated k-ras and wild type k-ras. Results showed that progression free survival was much better in patients with wild type k-ras than mutants. Therefore, k-ras mutation screening would be deemed mandatory prior to cetuximab treatment. Also, TS (thymidylate synthase) and ERCC1 (DNA excision repair enzyme) if over-expressed, make the patient resistant to platin treatment (FOLFOX Regimen). Therefore, patients who over-expressed ERCC1 should be switched to FOLFIRI treatment.

He also talked about the novel "Nab technology" which offers the ability to convert insoluble or poorly soluble drugs into protein particles, allowing them to become soluble and easier to deliver. It was started for pancreatic carcinoma, in which paclitaxel in the form of albumin bound nanoparticles, was found suitable for *in vivo* treatment. Nab paclitaxel is now indicated for breast cancer as a trial proved better response in albumin bound paclitaxel nanoparticles compared to polyethylated castor oil based paclitaxel.

He mentioned a recent study on SPARC (protein acidic and rich in cysteine) that could help oncologists in targeted therapy. SPARC is secreted by tumors, which binds albumin bound nutrients and concentrates them within tumor's interstitium to prevent nutrients from diffusing out of the cell. Drugs in similar way are bound to albumin and are delivered to the tumors. This is accomplished first by taking advantage of transport system across endothelial cells and then concentrating within tumor interstitium by its affinity to SPARC.

Dr Pant referred to another study on HER-2 neu and response to paclitaxel in node positive breast cancer in which the expression of HER-2 neu is associated with increased benefit on addition of paclitaxel after adjuvant treatment with doxorubicin plus cyclophosphamide regardless of estrogen receptor (ER) status. HER-2 neu negative, ER positive and node positive patients will derive little benefit. He also mentioned that "Oncotype DX21 Gene Assay" can predict recurrence score of ER/PR positive node negative treated breast cancer patients.

Dr Pant also briefed about how pharmacogenomics helps us plan personalised treatment by quoting a study in which tamoxifen's more potent metabolite, Endoxifen plasma concentrations were compared between groups of patients treated with anti-depressants and who were not treated with anti-depressants. It was observed that patients not on selective serotonin reuptake inhibitors had much higher levels of endoxifen in the blood.

He concluded that personalized therapy has been in use for quite some time and more research is needed to be able to optimally personalize cancer treatment.

Serrated Polyps and Colorectal Adenocarcinoma

Dr Robert E Petras, National Director for Gastrointestinal Pathology Services at AmeriPath Inc. & Medical Director and GI Pathology Fellowship Training Program Director at AmeriPath's Institute of Gastrointestinal Pathology and Digestive Disease in Oakwood Village, Ohio, delivered a talk on "The Serrated Polyp Family and Its Relation to MSI-H Colorectal Carcinoma" at Rajiv Gandhi Cancer Institute & Research Centre on August 24, 2009, which was attended by Director Medical, Consultants, DNB Candidates and Research Officers of the Institute.

Dr Petras talked about the genetic basis in colorectal cancer. Mutation in mismatch repair genes in DNA results in microsatellite instability (MSI). Almost all MSI-High cancers can be identified if the diagnostic panel includes MLH1, MSH2, PMS2 and MSH6. Gene sequencing is supreme investigation of choice. Patients with Lynch syndrome (hereditary nonpolyposis colon cancer syndrome) have increased risk for colon cancer; hence, they should be identified, screened and treated appropriately.

Hyperplastic polyps are benign polyps, most of which are classified as sessile serrated polyps and can be distinguished from invasive adenocarcinoma by the lack of infiltration and tumor desmoplasia. Morphologically, they are right sided, large, sessile and have poor endoscopic circumscription mimicking a mucosal fold. The type I serrated polyps are associated with MSI-H cancer in which there is methylation induced loss of expression of MLH1 and hence hyperplastic polyposis may be considered a "Mutator Phenotype" of MSI-H cancer. Sessile serrated polyps appear related to serrated adenomas and mixed polyps and could be the specific precursor lesion in sporadic MSI-H carcinoma. Methylation/mutation involved in serrated polyp family occur in genes MINT1, MINT2, MINT31, hMLH1, MGMT, KRAS and BRAF. A number of cytological and architectural abnormalities have been reported in the sessile serrated polyp, especially those that have been associated with carcinoma. Sessile serrated polyps should be treated by complete excision if possible.

Dr Petras concluded by stating that a shorter surveillance interval of 1-2 years would be prudent for these polyps that are incompletely excised or have remained unsampled.

Radiofrequency Ablation

Radiofrequency Ablation (RFA) of the tumor is an alternative option for local tumor control in which thermal energy, generated by passing high frequency current, is used for destroying the tissue. RFA is being used in Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC) mostly for unresectable liver tumors as well as osteoid osteoma and for a few cases of kidney tumors. Dr Nikhil Patel, Clinical Associate and Professor, Department of Imaging Science, University of Rochestor Medical Center, Rochestor, New York, and Associate Chief of Vascular and Interventional Radiology, Kenmore Mercy Hospital, Kenmore, New York, USA, delivered a lecture on "Radiofrequency Ablation in Kidney and Lung Cancers" on August 26, 2009 at RGCI&RC.

Dr Patel said that although the standard treatment for renal cell cancer has been partial or total nephrectomy, for small renal masses , RFA & cryotherapy can be used which have lesser complications than surgery. He explained the mechanism of RFA, management model adopted by them and highlighted some of the treated cases and their follow-up images showing good response. According to him, RFA acts best on tumor size < 3.7 cm and success rate was higher with exophytic tumors. Hydrodissection technique protects the colon from collateral thermal injury by injecting 5% dextrose between kidney and colon which acts as an insulator against high temperature generated by the procedure. Heat sink effect is prevented by embolisation of the vessels adjacent to the tumor in order to produce complete ablation.

RFA has a role in the treatment of both early stage primary lung cancer and metastatic lesions in selected group of patients. It is an excellent treatment option in candidates unsuitable for surgery and can be used alone or with radiotherapy. Dr Patel shared his experience of RFA on lung lesions. Major complications of RFA consist of pneumothorax or pleural effusion which are treated easily with drainage tube. PET-CT is the most accurate technique for patient follow-up and disease-free survival was seen for up to 2 years.

Dr Patel concluded by stating that RFA is an extremely safe procedure and an attractive option for local tumor control. It is a promising technique for treating many types of tumors of liver, lung, bone, breast and kidney and the radiologists need to play a principle role in its applications.

IN FOCUS

AUTOIMMUNE HAEMOLYTIC ANAEMIA

Introduction

After release from marrow, mature RBCs survive for 100 to 120 days in circulation. In the steady state, approximately 1% of the circulating erythrocytes are destroyed daily and are replaced by an equal number of new erythrocytes. The basic pathophysiology of the haemolytic anaemia is a reduced erythrocytes life span, ranging from nearly normal to remarkably shortened. In response to reduced RBC life span, the bone marrow increases its output of erythrocytes mediated via increased production of erythropoietin.

The haemolytic disorders can be classified according to whether the shortened RBC survival is an intrinsic abnormality of the erythrocyte or an extrinsic abnormality working on normal RBC. Intrinsic haemolytic anaemia generally results from inherited abnormalities of membrane, intracellular enzyme or haemoglobin. Extrinsic disorders usually are acquired and result from immunological, chemical or physical damage of erythrocyte. These two subtypes are not mutually exclusive.

Pathogenesis

Immune haemolytic anaemia is caused by IgG or IgM antibodies mediated destruction of RBCs via the complement system and reticuloendothelial system. It is classified as either autoimmune, alloimmune or drug induced, based on the type of antigen responsible for destruction. Autoimmune haemolytic anemia (AIHA) is characterized by the production of antibodies directed against high incidence antigens on self RBCs. Drug-induced antibodies can recognize either intrinsic RBC antigens or RBC bound drug. Antibodies that react with instrinsic RBC antigens are serologically indistinguishable from AIHA.The degree of haemolysis depends on characterstics of the bound antibody (e.g. quantity, specificity, ability to fix complement, etc) as well as the target antigen (density, expression, patient age). IgG-sensitized RBCs generally are eliminated by phagocytosis via reticuloendothelial system. On the other hand, IgM-sensitized RBCs generally are associated with a combination of intravascular and extravascular haemolysis. Autoimmune haemolytic anaemia due to the presence of warm agglutinins is almost due to IgG antibodies whereas cold agglutinins disease is due to IgM antibodies mediated activation of complement system.

Most cases of AIHA are idiopathic. Associated disorders may include: Lymphoproliferative diseases [e.g. chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma]; Preceding viral infection, usually in children; Autoimmune disorders [e.g. systemic lupus erythematosis (SLE)]; Drugs [e.g. penicillin etc]; Allogenic blood transfusion or haematopoietic transplantation.

Clinical Manifestation

The clinical symptoms in warm antibody type AIHA varies greatly with the amount of effective mass of the causative antibody. When the amount of antibody is small or the antibody is inefficient at effecting haemolysis, the patient may be asymptomatic. Most commonly, the patient may present with symptomatic anaemia. If the haemolysis is severe and of sudden onset, patient may present with symptoms of cardiac decompensation, inculding heart failure and/or chest pain. Physical examination usually reveals the presence of pallor and jaundice. Spleen is usually enlarged to a moderate degree.

Diagnosis

Accurate diagnosis requires the documentation of the presence of haemolysis along with demonstration of presence of a autoantibody on the surface of the patient's red cells. The MCHC on complete blood count is increased apart from low Hb, reflecting the presence of spherocytes. The absolute reticulocyte count is elevated in long standing anaemia, indicating the bone marrow response to anaemia. Laboratory finding indicating the presence of haemolysis include elevated levels of indirect bilirubin and LDH along with reduced levels of haptoglobin. The peripheral smear shows the presence of spherocytes usually with an increased number of polychromatic red cells (reticulocytes). The diagnosis of warm agglutinin AIHA is based upon detection of antibody on the surface of the RBC, usually by the direct coomb's test (DCT)/direct antiglobulin test (DAT). Majority of patients with warm agglutinin AIHA will inhibit a positive result with anti-IgG, anti-C3 or both. Etiologic factor needs to be investigated.

Treatment

The cause of warm agglutinin AIHA varies with age. In children, AIHA is usually a self -limiting disease, arising one to three weeks after a viral infection and disappearing within one to three months. In adults, the

disease is usually chronic and may variably manifest for months to years. The patients should be told of the chronic nature of the disease. Treatment of warm agglutinin AIHA is aimed at either reducing the amount of antibody being produced or reducing its efficiency in destruction of the red cells. Treatment should also be aimed at cessation of any possible offending drug and at any underlying disease, e.g. SLE or CLL.

Indications for Treatment

Most patients with AIHA present with an acute onset of severe haemolysis with symptomatic anaemia, requiring immediate treatment. In patient with underlying cardiac compromise, AIHA can present as a medical emergency, requiring immediate transfusions. Corticosteroids are frequently used as the first line therapy for warm AIHA, as they induce remission of antibody production in about 60-70% patients, but unfortunately, disease recurs in majority of patients. Once remission has been achieved, the steroids dose must be tapered. In children, this can be achieved quite rapidly since the disease process is often self-limiting. In adults, tapering should be more gradual. For patients not responding to corticosteroids or for those who require large doses of corticosteroids to maintain their response, elective splenectomy should be advised. For patient unwilling or unable to undergo splenectomy, treatment with rituximab or immunosuppressive/cytotoxic agents should be instituted. At present, there is not sufficient information to choose one of immunosuppressive/cytotoxic agents over another.

Cold Antibody Immunohaemolytic Anaemia

High titer of cold antibodies induce intravascular haemolysis with resulting haemoglobinemia and haemoglobinuria. The etiologic factors are usually some viral or mycoplasmal infections. These antibodies are of the IgM class and act via complement. Cold agglutinin disease is easily recognized by spontaneous agglutination and roulex formation on peripheral smear. Paroxysmal cold haemoglobinuria (PCH) is a rare condition associated with a specific type of cold antibody, the Donath Landsteiner haemolysin with anti-P specificity. Intravascular haemolysis is precipitated by low environmental temperature. PCH is now seen in children following exposure to viral infection and in adult as a part of autoimmune disorder.

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31st Annual Conference of the Association of Radiation Oncologists of India

Date: 26-29 Nov 2009
Venue: Hyderabad, India
Inf: Association of Radiation Oncologists of India
Fax: +91 40 2360 7530
E-mail: aroicon2009@hotmail.com
www.aroicon2009.com

21st International Congress on Anti-Cancer Treatment (ICACT)

Date: 02-05 Feb 2010
Venue: Paris, France
Inf: International Medical Events (IME)
Paris, France
Fax: + 33 1 47 43 2226
E-mail: infos@im-events.com
www.icact.com

6th International Conference Clinical Cancer Prevention 2010

Date: 18-20 March 2010
Venue: St Gallen, Switzerland
Inf: St Gallen Oncology Conferences
Fax: + 41 71 245 6805
E-mail: info@oncoconferences.ch
www.oncoconferences.ch

IPOS 12th World Congress of Psycho-Oncology

Date: 25-29 May 2010
Venue: Quebec City, QC, Canada
Inf: International Psycho-Oncology Society(IPOS),
Charlottesville,
VA, United States
Fax: +1 434 977 1856
E-mail: info@pos-society.org
www.ipos-society.org

4th World Congress of International Federation of Head & Neck Oncologic Societies (IFHNOS)

Date: 5-19 June 2010
Venue: Seoul, South Korea
Inf: IFHNOS
c/o Meci International Convention Services,
Inc. Seoul, South Korea
Fax: + 82 2 2082 2314
Email: ifhnos 2010@ifhnos2010.org
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