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From the Desk of Director Research

Magnetic Resonance Imaging (MRI) is a powerful imaging modality, having a unique place in oncology practice. It has been covered under the "Special Feature" in this issue. Scientists are unraveling the mystery of genes and pitching it as a 'Cure-all' medicine of the future. 'Perspective' deals with the potential role Gene Therapy can play in Cancer. The other regular features covered in the issue are: Research and Development, New Technologies, Clinical Trials, Watch- Out, Globe Scan, Cancer Control, and Research Department Activities.

Guest article on "Diet, Nutrition and Cancer", by Dr Kamala Krishnaswamy, describes the growing research in how diet and nutrition can modify the risk of cancer. An Emotional Support Group of Indian Cancer Society, the "Cancer Sahyog", has been profiled under another guest article by Mrs Indra Jasuja. A sincere and special thanks to Dr Kamala Krishnaswamy and Mrs Indra Jasuja for thair contributions.

"RGCON-2009", an annual event of the Institute, was held from March 27th to 29th ; a brief report on the event is given under "RGCON-2009: Highlights".

Special thanks are due 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.

Dr (Mrs) Ira Ray

CONTENTS

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SPECIAL FEATURE

MAGNETIC RESONANCE IMAGING IN CANCER CARE

Introduction

Cross-sectional imaging modalities like ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) form an integral part and are used in every phase of cancer care, be it screening, diagnosis, staging, treatment planning, therapeutic response evaluation or follow-up.

MRI is a powerful imaging technique that uses strong magnetic field and a radiofrequency pulse of appropriate frequency to generate cross-sectional images of any part of the body or a holistic whole body image. It is the desired combination of unmatched tissue contrast (that depicts different tissue types with great clarity) and high spatial resolution, that make MR images unique and of high diagnostic value. With evidence based practice as the hallmark in clinical oncology, MRI helps as a highly sensitive diagnostic tool for cancer detection, delineation of disease extent with greater clarity and provides a high certainty of diagnosis. Absence of ionization radiation with MRI is another feature that uniquely suits the frequent assessment peculiar to cancer management and a safe modality for the pediatric group.

Whole body MRI now takes minutes, making the whole body metastasis work up in oncology an attractive option. Interventional MRI guided biopsy is emerging fast in the field of early detection of cancer keeping with the fact that lesions are visualized much earlier in MRI and in many cases seen only in the MR with the best example being breast cancer. This helps in early detection of a lesion for early treatment that could result in cure. It is because MR-compatible interventional device has now become friendly and more accessible for sampling of early breast lesions in routine practice. While molecular imaging is evolving to enhance accuracy in diagnosis and help in targeted therapy at sub-cellular level, MR guided focused ultrasound therapy is making a break through entry into an entirely new field of non-invasive, non-radiation, non-surgical cancer therapy.

MRI Techniques in Cancer Management

The versatility of MR technology is evident from the fact that as a single modality, it unfolds many facets of cancer tissue and cancer biology relevant to cancer management. Besides unmatched anatomic information, MR images provide tissue vascularity (MR perfusion), neo-angiogenesis (pharmacokinetics of cancer tissue), metabolic (MR spectroscopy), cellularity and cell membrane turnover (tissue diffusion), functional MRI (fMRI) for assessing physiological functional areas in brain etc, noninvasively.

Contrast vs Spatial Resolution: MRI fully exploits its high inherent natural tissue contrast to advantage and is best appreciated in circumstances in which lesions occur within an organ without altering its exterior contour. This is more often true with liver lesions, lesion in cervix, oral tongue or small non-organ-deforming cancer in pancreas. Externally administered MRI contrast (gadolinium-based, etc) further enhances this ability with a much higher safety factor (low volume, low risk of allergy) than any iodine based contrast. Clinical advantages of the spatial resolution are mainly realized in situations when great contrast exists between lesion and background tissue, like in detecting contrast in small blood vessels ,etc. Time resolved contrast enhanced MR angiography does fairly well, as good as CT angiography, and provides results like digital subtraction angiography.

Serial Studies: Another important consideration is to make a clear distinction between imaging studies that are likely to be for single-use and serial investigations. Studies that are likely to result in serial reexamination may be better studied by MRI both for diagnostic accuracy and reasons of safety.

Whole Body MRI: Remote handling of examination table movement from the imaging console allows scan of the whole body without interruption and the evaluation software, taking care of the enormous image data generated to put across a panoramic view of the entire body from head to toe in about 15 minutes, as against 2 hours in the standard system. Data acquisition now employs multiple input channels with ever increasing number in the array of surface coils for high quality and high resolution images of multiple regions at a much faster rate. Time efficient parallel imaging is yet another major development that continually is improving the quality and speed of the MR scanners. Having achieved the necessary speed and diagnostically efficient work space, one major straight forward application of whole body MRI is in cancer staging.

***Functional MRI (fMRI)*:** fMRI studies based on the different magnetic properties of oxyhemoglobin and deoxyhemoglobin are being used increasingly for treatment planning in radiation oncology and surgical planning for intracranial tumors. The typical battery of tasks for neurosurgical planning includes hand tactile stimulation, hand-motor activity (finger-thumb tapping), picture naming (internal speech) and listening to the spoken word (language comprehension).

Perfusion MRI: MRI perfusion techniques help measure blood flow through tumor and has been used extensively to assess tumor angiogenesis and the response to therapy. In addition to perfusion, Dynamic Contrast-Enhanced Imaging is now being used to measure or extract parameters, such as cerebral blood volume, permeability of blood brain barrier, necrotic fraction, extracellular space volume and permeability- surface area product.

Diffusion Imaging: Diffusion-weighted imaging (DWI), a novel technique based on cellularity & cell membrane integrity, has shown an excellent tissue discrimination capability in a large number of disease conditions of liver, pancreas, renal and gastrointestinal tract. Whole body diffusion for soft tissue lesion along with whole body marrow imaging with STIR, hold a great promise in the staging work up of cancer as a matter of routine.

Magnetic Resonance Spectroscopy (MRS): Using MRS, the presence and concentration of various metabolites at micromolar levels can be measured. This technique exploits the phenomenon of "chemical shift" in the Nuclear Megnetic Resonance spectrum. MRS is useful in characterization of malignant growth with an unequivocal presence of high choline in general to more specific in certain tumors, like presence of alanine in meningioma.

MRI Emerging as a Screening Option: The biggest advantage of MRI to be accepted as a screening modality is that it does not use ionizing radiation and has high sensitivity for lesion detection. Several organ systems are currently imaged by MRI with an extremely high level of diagnostic accuracy, but screening protocol to include prostate, coronary vessels, colon, or breast still needs improvement where the current developments are focusing at.

Interventional MRI: To sample small lesions, MRI has a role in the field of image guided intervention. Breast biopsy devices fitted to existing MRI systems are commercially available. Dedicated MRI systems are now in place for brain surgery and guided biopsy for any part of the body.

Molecular Imaging: Molecular imaging is like sending little molecular spies into the body so that they can reside in desired molecular environment of specific targets, receptor sites and can be imaged or monitored from outside. MRI uses magnetically sensitive contrast for imaging purpose. In a host of areas, like lymph node and receptors, to study angiogenesis holds promise to be available as clinical tool that could enhance MR specificity and help drug delivery for targeted therapy. As sensitivity is the key to imaging, the transit of these low abundance biomolecules in the body would warrant technical breakthrough besides possible requirement of much high field MR systems.

MR Guided Tumor Ablation: MRI uniquely addresses various critical issues in thermal ablation therapy, like correct localization of tumor (target delineation), optimal targeting of the acoustic energy (treatment planning), real time monitoring of energy deposition and accurate control of the deposited thermal dose within the entire tumor volume (controlled delivery), all under image guidance. Though clear indications are yet to be defined for routine use, it has shown promise in dealing benign tumors and cancer of breast, brain, liver and prostate. The spectrum of application of this technique also extends to image-guided therapy using targeted drug delivery and gene therapy.

Imaging, Image Reading: MRI is extremely sensitive in detecting soft tissue changes. While some abnormal looking signal in the images needs to be ignored only from experience, others carry much relevance in the given clinical context and there are yet some others that relate to past history of the patient. Even though MRI is much better in characterizing various contents of the tumors, gross heterogeneity associated with tumor evolution in malignant tissue defies any attempt to make histological diagnosis. Till more research data is available on tissue characterization, leaving job of tissue diagnosis to the pathologist is a better practice in oncology.

MRI at RGCI&RC

MRI Department is an exclusive service facility at Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC). It is designed to provide high tech imaging modality optimally in the management of cancer. After more than a decade, it has a rich cumulated clinical experience of MRI in oncology, the largest database in

the country comprising a record number of more than 31,000 MRI case studies of various malignancies.

The MRI facility was updated in March 2008, with a state-of-the-art fully loaded 1.5 T MRI system [Magnetom Avanto (TIM), Siemens] to maintain the lead in the MRI practice in oncology in the country and provide necessary platform for high quality cancer research. The MRI system with its highest gradient subsystem, the best in the industry, coupled with the proprietary TIM (total imaging matrix) technology provides a full length of imaging with equal precision from "head to toe", a truly whole body to meet the challenges of cancer imaging and research. The evolved version of continuous table movement (TIM-CT) to be available in the department by the fall of the year, is poised to bring a quantum change in the speed of cancer imaging, a basic necessity for sick cancer patients.

Recently, the Institute's department of MRI has launched its world class "MR mammography program" to boost the existing breast cancer care under one roof. This has greatly helped in bridging the existing technology gap in the field with the west and provides comprehensive service with best of equipment and care under trained experts. With the introduction of the "MR guided breast biopsy" facility, the Institute has become the first and the only one at present to provide this service in the country. Since the MR guided biopsy facility is available, the whole spectrum of breast lesions, including the "only MR detected lesions", can be appropriately addressed. Early diagnosis and hence early treatment and cure as the cornerstone of breast cancer management, this pioneering effort will go a long way towards setting up of a dedicated breast care center in the country.

The department besides providing quality service, undertakes Research & Development activities that greatly help maintain a high standard. A few of these activities have proved visionary.

A visionary Digital Imaging and Communication in Medicine (DICOM) compliant Picture Archiving and Communication System (PACS) solution, developed in-house in 2002, is perhaps the first indigenous value added asset in the country. It has in fact helped in managing image records and in dispensing quality reporting. Besides this, it has provided necessary impetus for others to develop cost effective indigenous PACS solutions in the country, making healthcare delivery more effective and comprehensive across the enterprises. This work is a milestone achievement of RGCI&RC towards its commitment to the society. The Institute is making further efforts to enhance web-based capability and ready-to-deploy as homemade telemedicine solution, offer opinion, consultation and advice on health matters in order to deliver cost effective cancer management at patients doorsteps.

Further, the department has the distinction of having introduced "patient CD" for the first time in 1999, providing image data of patient in a CD ROM along with evaluation software that remains popular and effective means to browse on a personal computer anywhere. It is a visionary step to involve all those in the chain, using medical images in the healthcare delivery. The "MRI image bank"that holds MR image data from year 2000 till date without any interruption, continues to remain a unique service facility for reference, research and teaching.

The department has to its credit publishing a number of scientific papers in reputed international journals. The co-authored paper entitled "Handcrafted Fuzzy Rules for Tissue Classification", published in *Magnetic Resonance Imaging:* 2008, discusses the soft-computing technique, based on neural network and fuzzy logic, for tissue classification that could help early detection of white matter changes due to radiation therapy in brain tumor. The model is likely to trigger further research towards understanding dynamics of white matter demyelination as a result of radiation insult to normal brain. This literary work has earlier been awarded an Indian patent in 2005. Another scientific work entitled "Magnetic Resonance (MR) Patterns of Brain Metastasis in Lung Cancer Patients: Correlation of Imaging Findings with Symptom", published in *Journal of Thoracic Oncology:* 2008 , explains how a patient could remain asymptomatic even with large metastatic disease load in the brain, an observation that could change the present perception of managing lung cancer patients. This has influenced the management part in dealing such cases.

Conclusion

MRI is a powerful technique and has a unique place in oncology practice. It is, however, necessary that the practice be judicious and the interest of the patient kept above everything.

(Reviewed by Dr A Jena, Senior Consultant, Dept of Magnetic Resonance Imaging)

GUEST ARTICLE

DIET, NUTRITION AND CANCER

Introduction

Cancer is a major public health challenge to scientists as well as public health personnel today. Industrialization, rural/urban migration, dietary changes, excess consumption of tobacco and alcohol have added to cancer burden. According to certain estimates, there were 10 million new cancer cases and 7 million deaths in 2002 and it is estimated that in 2020 there will be 18 million of new cases, 10 million of which will die; and 70% of these will be in low income countries. Consumers are currently interested in prevention of all chronic disorders. Mounting research continues to indicate that food influences the ability to achieve one's genetic potential and also modifies the risk of a variety of disease conditions.

In India, the major cancers are tobacco related (lung, oral cavity, larynx, pharynx and oesophagus) in men and oral, oesophagus, lung (related to tobacco), breast and cervix in women. The incidence of oral cancers is the highest and in recent times, colon and prostate cancers have also increased. While the incidence of breast cancers in women is higher in urban India, cervical cancers predominate in rural segments. As cancer therapy is expensive, cancer prevention is of paramount importance in any healthcare policy, including cancer control. Simple lifestyle factors, such as smoking, drinking, unhealthy sexual practices, dietary patterns, body composition and physical activity, seem to play a significant role. Healthy dietary practices if adopted from a young age can aid significantly in prevention of several chronic diseases, including cancer.

Carcinogenic Process

Cancer is multifactorial and multi-mechanistic in its origin and pathogenesis, and requires multipronged approach for its control and management. Cancer is uncontrolled growth of cells where strictly regulated processes, such as cell division, differentiation and death, go out of control, resulting in tumour formation and dissemination. The genetic (DNA) damage or initiation and epigenetic complex process of promotion can lead to dysplasia (preneoplastic reversible changes) followed by carcinoma in situ, invasive carcinoma and metastatic carcinoma. Activation of oncogenes, loss of suppressor genes, dysfunctional intracellular communications, upregulated signal transduction, activation of transcriptional factors, deregulation of apoptosis, angiogenesis, inflammatory and oxidant damage and telomerase shortening characterize the process of cancer. This appears to be the common pathway of cancer.

Diet and Cancer

Current evidences indicate that dietary factors play an important role in inception, promotion and progression of cancer. It is estimated that almost one-third of cancers can be prevented by adopting appropriate diet around the globe. International variations in cancer rates are generally believed to be due to variations in life style factors and environmental exposures, of which diet and nutrients and bioactive phytochemicals in food appear to be important risk modifiers. Single ingredients or multiple ingredients of a particular food have been shown to impact several processes, including molecular events. A single dietary agent may alter multitude of processes, such as cell cycle, cell proliferation, cell death (apoptosis), cell differentiation, DNA damage and repair, inflammation and immunity, carcinogen metabolism and hormonal regulation. A typical diet can have more than 25000 bioactives with wide variations in amounts and bioavailability. Further, several food components and active ingredients may interact and influence the normal and cancer cells differently. The responses are likely to vary depending on the quantity (dose), timing and duration of exposure. Thus genomics, epigenomics, transcriptomics, proteomics and metabolomics can be influenced by diet and nutrient gene interactions. Finally, it may be the aggregate effects which manifest as protection in epidemiological studies.Thus, for prevention of harmful effects, it is necessary to consider evidence based science for public health policy.

Recommendations from Systematic Reviews of Institutions from USA, UK and Europe

The World Cancer Research Fund and American Institute for Cancer Research commissioned a study report on foods/nutrients and physical activity and prevention of cancer. A group of experts reviewed all the relevant research findings using meticulous methods, in order to generate recommendations to reduce the risk of cancer worldwide. A summary of the report is outlined here in terms of foods and drinks. The evidences have been categorised as convincing, probable, suggestive and limited, based on strength of evidences, mostly epidemiological though experimental information has not been ignored.

1. Since obesity, ie, higher body mass index and abdominal fat and total body fat have been found as causal agents(convincing/probable evidence) for several cancers, it has been suggested that body mass index (median) be maintained between 21 and 23, depending on the normal range for different populations. Weight gain and increases in abdominal fat should be avoided throughout adulthood. There is only limited evidence suggesting that diets relatively high in fats and oils (in total, or any type) are in themselves a cause of any cancer. Scanty evidence suggests that total fat is a cause of lung cancer and of postmenopausal breast cancer. Suggestive evidence shows foods containing animal fat cause colorectal cancer. Both the roles of carbohydrates and fat are mediated through overweight and obesity.

2. It is necessary to maintain average physical activity above 1.6 PAL. Individuals must maintain physical activity such as moderate walking for 30 min/day and build it up for 60 min. All sedentary habits need to be avoided, like TV viewing and other such leisurely activities.

3. In order to prevent obesity, it is necessary to consume average energy dense foods (125kcal/100g) and avoid sugary drinks and high energy foods (225-275 kcal/ 100g), such as processed and fast foods which can increase glycaemic index and load.

4. It is best to consume unprocessed plant based foods to provide non-starch polysaccharides (fibre) 25g/day. Whole grain cereals, pulses, vegetables and fruits will provide adequate fibre to protect against several cancers. Foods containing micronutrients, such as beta carotene, vitamin C, selenium and phytochemicals such as lycopene are considered important in prevention of cancer.

5. It is essential to limit the intake of cooked red meat(500g/week) and avoid processed meat (smoked, cured, salted or chemically preserved). There is suggestive evidence that fish, and also foods containing vitamin D, protect against cancer.

6. There is a strong relationship between alcohol and cancer and causality has been established for upper aerodigestive, colorectal and breast cancer. Therefore men should limit alcohol consumption to two drinks/d and women to one drink (10-15g of ethanol/d).

7. Fresh vegetables /fruits (preferably green and yellow ones) to be used in plenty after thorough washing (400-500g/d/person). Processing to be minimal and free from contaminants and harmful chemicals.

8. One should avoid mouldy grains as they are sources of aflatoxin.

9. Salt intake should be less than 6g/d/ person(2.4g of sodium), including processed food.

10. Nutritional needs must be satisfied through a diversified diet. Nutritional or dietary supplements are not advised.

11. Exclusive breast feeding protects both the child and the mother against cancer.

12. Cancer survivors must receive nutrition care from trained persons. Regular physical activity and measures to control weight may help prevent recurrence of breast cancer. High doses of micro and phytonutrients are not indicated.

Dietary Guidelines for Prevention of Cancers

The guidelines are consistent with good dietary practices which if followed would not only reduce the incidence of cancer but would also limit other chronic diseases, such as cardiovascular problems and diabetes.

- Body mass index should be between 21-23 and gain in weight and deposition of abdominal fat throughout adulthood should be restricted.
- Physical activity should be regular and maintained.
- Unprocessed whole grains and pulses as sources of energy and protein with fat intake not exceeding 25-30% of total calorie will provide all macronutrients.
- Fresh vegetables/ fruits (preferably green and yellow ones) in plenty to be used after thorough washing.
- Contaminated foods, specially fungal and fried, burnt, smoked, fermented, salted and pickled foods should be avoided.
- Alcohol consumption and hot beverages to be used moderately.

All nutrients should be obtained through a diversified diet and not through dietary supplements.

Suggested Readings

- John A. Milner: Diet and Cancer-Facts and Controversies. *Nutrition and Cancer*, 56(2),216–24; 2006.
- Kim YI: Nutrition and Cancer.*In* Bowmann BA, Russel RM (eds): *Present Knowledge in Nutrition*. Washington DC; International Life Science Institute. P 688-719, 2006.
- World Cancer Research Fund/ American Institute for Cancer Research: Food, Nutrition, Physical Activity and the Prevention of Cancer- A Global Perspective. Washinton,DC; AICR; 2007.

(Kamala Krishnaswamy, Former Director, National Institute of Nutrition & Former President, Nutrition Society of India)

GUEST ARTICLE

CANCER SAHYOG

Cancer Sahyog is an Emotional Support Group of Indian Cancer Society (ICS). One breaks into a cold sweat at the very mention of the word Cancer! It seems invincible, leading to the feeling of helplessness when a diagnosis is made. Doctors dealing with the Big C day after day sometimes fail to realize what this pronouncement means to the patient or his family .

Cancer Sahyog took up the cudgels in a unique field from which other NGO's shy off. The idea has been to induct survivors as members to provide emotional support to the cancer patients and their families. Who can better understand the trauma, or the pain experienced by a Cancer Patient than a Cancer Survivor? Similarly, who can better address the worries of families than a caregiver who himself has lived through the experience? The inception of the Emotional Support Group in February 1991 by a few brave cancer survivors and caregivers under the umbrella of ICS marked a milestone event. Cancer survivors thus entered the arena to support and comfort fellow travelers in today's clinics (Sahyog = Fellow travelers). They became **Sahyogis,** adding a dimension of grace and care to mere physical treatment.

The birth of support groups started from the need to share and receive succour. It is rightly said that only the diver knows the depth of the sea and it is this adage, which is the basis of support groups. Every patient feels that his pain and discomfort is unique and surpasses everyone else's. There is the thought "How can you possibly know what I am going through?" That is where the survivor steps in, someone who has walked through a similar situation, faced the onslaught of the disease and its accompanying treatment, gone through similar fears and anxieties.

Cancer Sahyog has about 80 members. Most of them are either survivors or caregivers; some of them are doctors and a few associate members who help in administrative or Public Relation work. The survivors and caregivers of Cancer Sahyog span the different cancer hospitals in Delhi and NCR. The volunteers work as a bridge between the doctor and the patient. These cheerful faces can be found in OPD's and wards, tirelessly carrying out their task of cheering up the depressed and anxious patients and their equally stressed out families. The purpose of Cancer Sahyog is to provide emotional support, the ability to empathise with anxieties and fears, and find ways to help patients and families to deal successfully with them.

Ignorance is a curse. Medical questions are not their forte but the basic knowledge about food, exercise, a positive mindset, and disease is imparted through literature, which is distributed in all the hospitals. These give correct information and answer to many questions arising in the mind of the patient and his caregivers.

Cancer Sahyog's activities are multifaceted. They help ICS in spreading awareness through talks on radio and TV, and awareness programmes in the Shopping Malls during the breast cancer month of October. The members actively work for the Survivor's Walk for Cancer Awareness held every year on first Sunday of February. They organise an annual seminar in the first week of October every year which deals with a particular subject concerning cancer survivors. It may be medical, or psychological, or even relating to survivorship. Over the years, it has been realized that there is another field in which Cancer Sahyog could extend a helping hand, ie financial assistance towards treatment. A lot of patients cannot afford the extremely expensive medicines, so Cancer Sahyog helps them with the procurement of the same. Medical assistance is based on a strict protocol of needs assessment. The patient has to meet certain criteria in order to get such help.

There was a lot of skepticism in the medical fraternity when Cancer Sahyog began its mission but with the passage of time and their volunteers' ability to establish their sincerity and credibility, the doctors in different hospitals have realised the selfless devotion with which they work. Their contribution is now being recognized and it has made a niche in the hearts of the patients, their families and the doctors. Volunteers visit different cancer hospitals where they help the patients with information, medicines and empathy. They encourage them to become strong beings physically, mentally and emotionally. They leand support to the families by untiringly answering their queries about disease, food and the problems arising out of the treatment. The volunteers steer them in the right direction, ensuring success for both – igniting the will to live, the joy of living and the determination to defeat the monster of cancer.

(Mrs Indra Jasuja, President, Cancer Sahyog, Indian Cancer Society, Delhi)

PERSPECTIVE

GENE THERAPY IN CANCER

Introduction

Gene therapy is the insertion of genes into an individual's cells and tissues to treat a disease, such as a hereditary disease in which a deleterious mutant allele is replaced with a functional one. Although the technology is still in its infancy, it has been used with some success. The main objective in gene therapy in cancer is the development of efficient, non-toxic gene carriers that can encapsulate and deliver foreign genetic materials into specific cell types such as cancerous cells. Scientists are focusing on both therapeutic genes and genes to produce a systemic immune reaction against micrometastases. It is also being investigated as part of a combination treatment to treat primary tumours and metastases and as a chemo- and radiation-sensitizer.

Gene Therapy Procedure

At present, the most widely used gene therapy procedure follows these steps:

i) Identification, isolation and amplification of the gene to be used in the treatment;
ii) Extraction and in vitro culture of tissue cells from the patient to be treated;
iii) Transfer of the therapeutic gene into these cells via a vector, using a gene that contains a promoting sequence to enable its expression and a marker to identify cells into which it is incorporated; and
iv) Transfer into the patient of selected gene-containing cells. The theory is that when the gene exerts its normal physiological functions, the disease will be eliminated.

Viruses used for oncolytic cancer therapy include adenoviruses, vaccinia, herpes simplex type 1, Newcastle disease virus, measles, retroviruses, vesicular stomatitis virus and reoviruses. Nonviral vectors, including polymers, liposomes, stem cells and artificial chromosomes may be safer than some viral vectors because they do not cause the same immune reactions, but the downside to liposomes can be inefficient entry sof DNA into the cell's nucleus.

Gene Therapy Approaches

Current gene therapy approaches include:

i) Addiction gene therapy: Tumour suppressors introduced into tumour cells by gene transfer are p53 gene, Rb (retinoblastoma gene) and mda-7 (melanoma differentiation-associated gene-7) and Allovectin-7®.

ii) Gene therapy using oncolytic viruses: Oncolytic viruses replicate only tumour cells, and attenuate its toxicity in normal tissue.

iii) Suicide gene therapy: Genes are introduced to stimulate the generation of products that are toxic for the cells and contribute towards resistance against chemotherapy.

iv) Introduction of genes to inhibit tumour angiogenesis: Research is in progress on the use of microencapsulated cells in angiogenic cancer therapy.

v) Immunotherapy: The aim of immunotherapy is to increase the patient's immune response to the tumour.

vi) Excision gene therapy: The aim of this therapy is to remove defective oncogenes, thereby inhibiting the growth of tumour cells.

vii) Antisense RNA: Antisense RNA may prevent the activity of oncogenes, including myc, fos and ras; and it can also inhibit viruses, e.g., HSV-1, HPV (Human Papillomavirus) and HTLV-1 (Human T-lymphotropic virus).

Major Developments

Scientists have successfully treated metastatic melanoma in two patients using killer T-cells genetically retargeted to attack the cancer cells. Gene therapy has also been used successfully to treat two adult patients for a disease affecting myeloid cells. Positive phase III trial results with Advexin which targets the cancer suppressor gene p53 and although this single-gene approach is finally having success, two decades of research has led scientists to believe that replacing one gene may not be the best strategy in multigenic disease like cancer. Newer approach is focusing on both therapeutic genes and genes to produce a systemic immune reaction against micrometastases.

Treating metastases: Some researchers are focusing on gene therapy as a better approach to treating metastases. The results of a trial testing a tumour-targeted gene transfer treatment, Rexin-G, showed antitumour activity in several metastatic cancers. It is now designated as an orphan drug in the US for osteosarcoma, soft-tissue sarcoma, and pancreatic cancer. Rexin-G showed lack of systemic toxicity, reduction of tumour burden, and enhanced quality of life.

Reximmune-C, designed as an immune stimulant, or vaccine, is used alone or in combination with Rexin-G.

Preclinical studies and phase 1 testing of the combination in several cancers showed greater cancer cell death than that achieved with Rexin-G alone. This combination of gene therapy kills cancer cells, there by exposing new tumour antigens, while promoting a local immune response. A newer version of Reximmune-C has a "off switch" as an additional safeguard, a herpes simplex, thymidine kinase suicide gene.

Immunotherapies: An experiment, called adoptive cell transfer that genetically engineered the lymphocytes of 17 patients with certain T-cell receptors by using a retrovirus, enabling cells to recognize tumour cell surface proteins and kill cancer cells, was hailed as the first successful use of gene therapy to treat cancer. Additional T-cell receptors that recognize common epithelial cell cancers, such as breast, ovarian, and colon cancer, were identified. In a different approach to treat chronic lymphocytic leukemia, patients' CD 40 B-cells were infected with its ligand, CD-154, by using an adenoviral vector, which enhances antigen specific immune recognition by autologous T-cells. Recently, an improved human version of CD-154, called ISF 35, has been developed which is under clinical trial.

Oncolytic viruses: Oncolytic viruses are now one of the most active areas of gene therapy research in cancer, with several proof of principle studies ongoing.Early oncolytic viral therapy focused on intratumoral injection for head & neck cancers and gliomas. Researchers tried next to give oncolytic viruses intravenously. Several oncolytic viruses are in early stage of testing as well as in combination with chemotherapy and radiation. Modified vaccinia virus and products from the rhabdovirus family destroy tumors by multiple mechanisms, including viral lysis, tumour vascular shutdown and induction of a systemic immune response to cancer. Oncolytic viral gene therapy increases vascular permeability, inflammatory gene expression and leukocyte infiltration, however, administering one dose of an antiangiogenic peptide before treatment counteracts angiogenesis and enhances the virus efficacy.

Oncolytic viruses also have the potential to be self-amplifying drugs that can spread to other cancer cells. This amplification has the ability to spread cell killing and amplify the production of transgene proteins and immune responses by producing cytokines or antigene. Reolysin, an unmodified human reovirus, is also being tested in a range of solid tumours and metastatic cancer as a monotherapy and in combination with chemotherapy and radiation, with local or systemic delivery. Oncolytic viruses could thus play an important role in gene therapy for cancer.

Multiple Challenges

Emerging challenges of gene therapy are: determining which genes are likely to be most effective to treat tumours and metastases and whether local or systemic administration is best; discovering and optimizing new vectors best suited to the type of issue being targeted, improving gene expression, and reducing toxicity. About 70 percent of gene transfer treatments to-date are viral. There are many safety issues associated with their use. Viruses administered even locally have been detected in remote, non-targeted tissues, such as reproductive organs. Improperly disabled viruses can trigger exaggerated immune reactions in patients with an underlying disease.

The viruses can also insert themselves into the wrong sites, which has caused cases of leukemia in children being treated for severe combined immunodeficiency disease. Another weakness of viral vectors is that, like viruses, a patient's immune system can disable them. New viral vectors are being engineered to remain in the body longer, produce long term gene expression and have better safety profiles. Another strategy to enable viral vectors to avoid immune detection is to disguise them by using polyethylene glycol "stealth" coatings, enabling both carrier and gene to remain in circulation longer before the body destroys them.

Conclusion

Cancer gene therapy is the most studied application of gene therapy. Overall, the experiences from the major developments and research till date suggest that (a) human clinical studies provide the ultimate test to defining limits of current strategies; (b) information from these trials can guide the rational address of current system limits; and (c) derived advanced generation systems can provide truly impressive gains in the therapeutic potential achieved. It is hoped that these central lessons represent a pivotal paradigm for future endeavors in this field so that true "therapeutic" results can be reported in cancer gene therapy, and that cancer gene therapy joins the ranks of gene therapy successes.

(Reviewed by Dr Suresh P, DNB Student, Dr Ullas Batra, Assoc Consultant and Dr D C Doval, Senior Consultant, Dept. of Medical Oncology)

RESEARCH AND DEVELOPMENT

Larynx Preservation

Many patients with locally advanced laryngeal and hypopharyngeal cancer face total laryngectomy, a procedure that comes with difficult side effects. Normal speech is often totally affected. French researchers have found that treating locally advanced laryngeal and hypopharyngeal cancer patients with a 3-drug chemotherapy combination helps many patients avoid surgery and keep their larynx and in turn, improve their quality-of-life.

Patients were randomly assigned to either a combination of cisplatin and 5-fluorouracil (5-FU) or docetaxel, cisplatin and 5-FU. Those who responded to the chemotherapy underwent radiation therapy; those who didn't had surgery. After 3 years they found that about 70% of the patients who got docetaxel in addition to the other drugs were able to keep their larynx, compared to about 58% in the other group. More patients in the docetaxel group also had their tumors shrink significantly with chemotherapy (80% versus 59.2%) though they experienced more of certain side effects. The researchers did not find any difference in survival between the two groups.

(ACS News, Mar 25, 2009)

New Alternative to Biopsy

According to researchers at the Stanford University School of Medicine, a drop of blood or a chunk of tissue may one day be all that is necessary to diagnose cancers and assess their response to treatment. The scientists used a specialized machine capable of analyzing whether individual cancer-associated proteins were present in the tiny samples and even whether modifications of the proteins varied in response to cancer treatments. Although the study focused on blood cancers, the hope is that the technique might also provide a faster, less invasive way to track solid tumors. They were able to detect varying levels of expression of two common oncogenes in 44 of 49 lymphoma samples from human patients as compared with normal controls and even distinguish some types of lymphomas from others. If one can figure out how to go in with a needle and remove just a few cells for analysis, repeated assessments can be made as to how the tumor is responding to the treatment. This is really a complement to the existing diagnostic and therapeutic methods.

(Science Daily, Apr 12, 2009)

Salivary Diagnostics

Researchers showcased a remarkable spectrum of research outcomes that expand the clinical applications of saliva based on 'diagnostic toolboxes', as well as establish foundational mechanistic insights into salivary diagnostics. The scientific and translational values of three diagnostic toolboxes (proteins, DNA, and RNA) were highlighted in the saliva. One research team established the systemic phosphoproteome documentation technology, providing a powerful tool to evaluate health *vs.* disease states of oral and systemic disease. Another group explored the methylation status of genomic DNA contents providing proof-of-concept data that differential methylation analysis of specific cellular genes in saliva can be used to detect oral cancer. A third diagnostic alphabet, the salivary transcriptome, was discovered providing the scientific rationale for the translational utilization of the salivary transcriptome for biomarker studies. The mechanistic insights into the value of salivary diagnostics for systemic disease detection demonstrated that hormones/lymphokines/cytokines produced by tumors will lead to transcriptional profile changes and ectopic protein translation, which will be secreted into saliva as tumor-associated surrogate biomarkers.

(Medical News Today, Apr 4, 2009)

TheraSphere® for Liver Metastases

Among patients with colorectal cancer that has spread to the liver, treatment of the liver with TheraSphere® (yttrium-90 glass microspheres) appears to provide sustained stabilization of the disease. Microscopic glass beads that contain a radioactive material are delivered through a catheter into the hepatic artery. The beads become trapped in the blood vessels that feed the tumor and deliver radiation to the tumor. To explore the safety and efficacy of TheraSphere® among patients with colorectal cancer that has spread to the liver, researchers conducted a study among 72 patients with liver metastases that could not be surgically removed. Patients received an average of two Therasphere® treatments. A reduction in the metastases liver was experienced by 40% of patients. Cancer progression in the liver occurred at a median of 15.4 months after first treatment, indicating TheraSphere® may eventually expand the treatment options available to patients with liver metastases.

(Cancer, Mar 6, 2009)

NEW TECHNOLOGIES

DIAGNOSTICS

Diagnostic for Melanoma

Researchers at the University of California, San Francisco, have developed a new diagnostic technique to distinguish benign moles from malignant melanomas by measuring differences in levels of genetic markers. To develop the diagnostic tool, they first used a microarray, a "gene chip", to identify about 1,000 human genes present in malignant melanomas as and benign moles. They narrowed their study down to five genes that all showed higher levels of activity. They stained the proteins with antibodies to assess the level of gene expression in mole and melanoma tissues and found that the increased protein production by the melanomas compared with the moles was statistically significant and thus a reliable diagnostic indicator. The proteins also showed different patterns of activity in the two types of tissue, yielding a second, even more discriminating diagnostic indicator. The strategy correctly diagnosed 75% of the most difficult cases which had previously been misdiagnosed. The technique also accurately diagnosed other difficult-to-diagnose moles, known as dysplastic and Spitz nevi.

(Medical News Today, Apr 1, 2009)

New Cell Imaging Technology

A new imaging technique that uses tiny, dye-containing particles to "fingerprint" proteins within a single cell may lead to better ways to diagnose and treat cancer. The technique could improve the ability not only to diagnose cancers and distinguish different types of cancer cells from each other, but to determine how aggressive a tumor is and how likely it is to respond to therapy. Current cell imaging technology, known as flow cytometry, uses antibodies tagged with fluorescent dye to detect proteins, which light up as they flow through a beam of light. The images can, however, become muddy if there are too many overlapping colors, limiting the number of proteins that can be imaged simultaneously. Rather than simple fluorescent dyes, the team used special nanoparticle probes created by Intel Corp that give off distinct signals. Instead of giving a very broad, smooth spectrum they give sharp fingerprints and detect specific proteins in a single cell. The team hopes eventually to be able to image as many as 100 distinct features inside a cell.

(Reuters, Apr 14, 2009)

Pathwork Tissue of Origin Test

To determine the tumor's origin, the Pathwork Tissue of Origin test uses microarray technology to measure the gene expression pattern, comprising more than 1,500 genes, in a tumor with an uncertain origin and compares it with expression patterns of a panel of 15 known tumor types representing 90 percent of all solid tumors and 58 morphologies overall. The Tissue of Origin test can benefit physicians by allowing them to diagnose tumors with uncertain origins with greater confidence because the test provides objective data and the ability to both rule in and rule out tumor types.

The results of the 547-specimen study showed that the test has significant potential to reduce diagnostic uncertainty for poorly differentiated, undifferentiated or metastatic tumors. To- date, no other tests in this category have undergone as large a clinical validation study or produced such strong results. Both the frozen and formalin-fixed, paraffin-embedded versions of the test are commercially available as a service through Pathwork Diagnostics Laboratory.

(Pathwork Diagnostics, Mar 31, 2009)

Test for Metastatic Risk

Researchers at NewYork-Presbyterian Hospital/ Weill Cornell Medical Center have identified a new marker for breast cancer metastasis called Tumor Microenvironment of Metastasis (TMEM). Density of TMEM was associated with the development of distant organ metastasis, independent of lymph node status and tumor grade. TMEM density directly reflects the blood- born mechanism of metastasis and therefore may prove to be more specific and directly relevant. This development could change the way breast cancer is treated. If patients can be better classified as either low risk or high risk for metastasis, therapies can be custom tailored to patients, preventing over-treatment or under-treatment of the disease.

A retrospective analysis of tissue samples from 30 breast cancer patients showed that TMEM density was more than double in the group of patients who developed systemic metastases compared with the patients with only localized breast cancer. Offering further evidence in support of the TMEM concept, they found that in well-differentiated tumors, where the outcome is generally good, the TMEM count was low.

(J Clinical Cancer Research, Mar 24, 2009)

DRUGS

Drug for Osteosarcoma

The European Commission has approved MEPACT (mifamurtide, L-MTP-PE), an immune-based therapy for pediatric patients with non-metastatic, resectable osteosarcoma. The approval is based on clinical studies led by researchers at the University of Texas M. D. Anderson Cancer Center and a national co-operative group. Getting approval in Europe is a huge milestone for fighting pediatric cancer. MEPACT when combined with chemotherapy, resulted in approximately a 30 percent decrease in the risk of death with 78 percent of patients surviving more than six years following treatment. This therapy is the first in more than 20 years to improve the long-term survival of osteosarcoma patients. MEPACT works by stimulating certain white blood cells, called macrophages, to kill tumor cells. The chemotherapy acts like a bomb sent in to destroy the tumor, while MEPACT acts as a special forces unit sent in to clean out any remaining pockets of microscopic disease. Relapsed osteosarcoma is often resistant to chemotherapy. By giving MEPACT to newly diagnosed patients, relapse can be prevented by taking care of any remaining tumor cells after chemotherapy.

(M.D. Anderson News Release, Mar10, 2009)

Kidney Cancer Drug

The US Food and Drug Administration has approved targeted cancer therapy Afinitor oral tablets (everolimus) for the treatment of an advanced kidney cancer in patients where the disease continued to progress after treatment with other drugs. Afinitor is a kinase inhibitor; it stops tumors growing by blocking a specific protein called mTOR. This action stops the cell to cell communications that help cancer cells to grow, divide and metabolize. The FDA approval relied on the results of the RECORD-1 clinical trial that tested the safety and effectiveness of Afinitor given as daily oral dose against placebo. The trial was stopped early because interim results showed that patients taking the drug experienced delayed tumor growth and spread compared to those who did not. Disease progression was delayed for about five months in 50 percent of the patients who took the drug compared to only 2 months for those who did not. This approval provides a new and useful tool for treating advanced renal cell cancer, representing an important step forward in managing this disease.

(FDA, Novartis, Mar 31, 2009)

Novel Lung Cancer Vaccine

An experimental vaccine, called MAGE-A3 antigen-specific cancer immunotherapeutic that triggers the patient's immune system to identify and attack specific tumor cells, has shown new promise for the treatment of early lung cancer without harming normal cells. A total of 182 patients with non-small-cell lung cancers were included in the early phase of the study sponsored by GlaxoSmithKline which is developing the vaccine therapy. All the patients had cancers expressing MAGE-A3. After having surgery to remove the tumors, 122 patients were randomly assigned to treatment with the MAGE-A3-targeting vaccine and 60 patients received placebo vaccines. Patients were given five injections every three weeks at the beginning of treatment and then eight injections every three months later for a total of 27 months. The preliminary research showed that the treatment was well tolerated by patients and the MAGE-A3-treated patients seemed less likely to have recurrences and die from the disease than the placebo-treated patients. Further studies need to be conducted to test the safety and efficacy of the vaccine.

(Rush University Medical Center, Apr 7, 2009)

REOLYSIN®

REOLYSIN® is being developed from the naturally occurring reovirus by Oncolytics Biotech Inc. The reovirus preferentially replicates in cancer cells with an activated RAS pathway, while sparing normal cells. Approximately two-thirds of all cancers have an activated RAS pathway, including most metastatic disease. Viral replication within cancer cells causes them to burst open, releasing more viruses to infect other cells.

REOLYSIN® has demonstrated impressive results in clinical trials on its own, but particularly in combination with certain chemotherapeutics. Recently, Oncolytics announced positive results from three combination REOLYSIN® and chemotherapy trials. The trials included Phase I/II UK trial of REOLYSIN® combined with paclitaxel/carboplatin for patients with advanced head & neck cancers; second trial using combination REOLYSIN® and the docetaxel for patients with advanced or metastatic solid tumors that are refractory to standard therapy or for which no curative standard therapy exists; and third clinical trial using REOLYSIN® in combination with gemcitabine (Gemzar®) for advanced cancer patients.

(Oncolytics Biotech, Apr 4, 2009)

CLINICAL TRIALS

First Phase 0 Oncology Trial

Phase 0 trial focuses primarily on tolerance and the ability of the drug to hit a target. Low success rate of new therapies for the treatment of cancer has necessitated revaluation of the standard anti-cancer drug development paradigm, of which phase 0 trials would be a key part of a new approach. Scientists at the National Cancer Institute conducted the first phase 0 clinical trial of a drug, ABT-888 with chemotherapy drug, involving 13 patients with advanced cancers, administering a small single oral dose of 10, 25 or 50 mg ABT-888. The results demonstrated the statistically significant inhibition of enzyme activity in the patient tumor samples and blood cells, showing the drug affected its target and was well tolerated, thus providing an initial example of a new paradigm for early therapeutic development in oncology. Most importantly, this trial showed that it was possible to enroll a small number of patients, treat them with a low dose of a new drug, identify whether the desired target of the drug was effective, and obtained all this critical information relatively quickly.

(NCI News, Apr 13, 2009)

Myelodysplastic Syndromes

According to Phase III clinical trial, treatment of patients with higher-risk myelodysplastic syndromes (MDS) with Vidaza® (azacitidine) resulted in better survival than conventional care . MDS are a group of blood (hematologic) disorders. Vidaza® was first approved for the treatment of MDS in 2004, based on improved response rates and reduced need for transfusions. Prior to the current study, there was no conclusive evidence that Vidaza® improved survival. The current study (AZA-001) involved 358 patients with higher-risk MDS, treated with either Vidaza® or conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy). Results showed that median overall survival was 24.5 months for patients treated with Vidaza® compared with 15 months for those treated with conventional care. The two years survival was nearly 51% for patients treated with Vidaza® compared with 26.2% for those treated with conventional care.

(CancerConsultants.com, Mar 6,2009)

Rectal Cancer Recurrence

For patients with operable rectal cancer, surgery is a standard approach of treatment. To reduce the risk of cancer recurrence, patients with Stage II or Stage III rectal cancer may also receive additional treatment with chemotherapy and/or radiation therapy which may be given before surgery (neoadjuvant), after surgery (adjuvant), or both.To compare the two different approaches to the treatment of operable rectal cancer, researchers in four countries (the UK, Canada, South Africa and New Zealand) conducted a clinical trial among 1,350 patients with operable rectal cancer. Patients were randomly assigned to one of the two treatment groups. One group was given a short (one-week) course of neoadjuvant radiation therapy; some patients in this group also received adjuvant chemotherapy and the other group was given selective adjuvant chemoradiotherapy.The results indicated that patients assigned to the neoadjuvant radiation therapy group had a lower risk of local recurrence.After three years 4.4% of patients in the neoadjuvant radiation therapy group had developed local recurrence compared with 10.6% of patients assigned to the selective adjuvant chemoradiotherapy group, suggesting that short-course preoperative radiotherapy is an effective treatment for patients with operable rectal cancer.

(Lancet, Mar 7, 2009)

Temodar® for Brain Cancer

Glioblastoma multiforme (GBM) is the most common and fatal type of primary brain cancer. The European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada Clinical Trials Group (NCIC) conducted a randomized, Phase III trial to evaluate the effects of radiation plus chemotherapy with Temodar® (temozolomide) in patients with glioblastoma. A total of 573 patients were randomly assigned to receive radiation alone or radiation with concurrent Temodar®, followed by up to six cycles of adjuvant Temodar®. After five years of follow-up,in the group of patients treated with Temodar and radiation, 27.2% were alive at two years, 16% at three years, 12.1% at four years and 9.8% at five years. Of those treated with radiation alone, 10.9% were alive at two years, 4.4% at three years, 3.0% at four years and 1.9% at five years, indicating that the combined treatment with radiation and chemotherapy improved survival.

(Lancet Oncology, Mar 9, 2009)

WATCH-OUT

Breast Cancer

United States Patent and Trademark Office has issued patent No 7, 514, 209 to Dai Hong Yue et al. The assignees are Rosetta Inpharmatics LLC (Seattle, WA) and Netherlands Cancer Institute. The patent is entitled 'Diagnosis and Prognosis of Breast Cancer Patients'; published on April 7, 2009. The invention relates to the identification of marker genes useful in the diagnosis and prognosis of breast cancer. More particularly, the invention relates to the identification of a set of marker genes associated with breast cancer, a set of marker genes differentially expressed in estrogen receptor (+) versus estrogen receptor (-) tumors, in BRCA1 versus sporadic tumors, and in sporadic tumors from patients with good clinical prognosis versus patients with poor clinical prognosis . For each of the marker sets above, the invention further relates to methods of distinguishing the breast cancer-related conditions. The invention further provides methods for determining the course of treatment of a patient with breast cancer. The invention also relates to kits containing ready-to-use microarrays and computer software for data analysis using the statistical methods disclosed herein.

(USPTO, Apr 16, 2009)

Cervical Cancer

Mackay Memorial Hospital [TW] has been assigned Patent No. US2009082437 (A1) entitled 'Use of Oxaliplatin for Enhancing Radiosensitivity in Radiotherapy of Cervical Cancer' published on March 26, 2009. The present invention relates to a method for enhancing radiosensitivity in radiotherapy of cervical cancer by administering an effective amount of oxaliplatin to cervical cancer cells. Radiation combined with pretreatment of oxaliplatin according to the present invention helps to enhance the cytotoxicity of radiation and results in augmenting radiation-induced mitotic catastrophe. The analysis on molecular mechanism revealed that oxaliplatin augmented the radiation-induced DNA double-strand break indicated by reducing gamma-H2AX expression, abrogated radiation-induced ATM phosphorylation and reduced the Chk2 phosphorylation. Oxaliplatin can be used as a promising radiosensitizer for treatment of cervical cancer in radiotherapy.

(esp@cenet.com, Apr 17, 2009)

Gene for Colorectal Cancer Screening

Although methods for detecting colon cancer exist, the methods are not ideal. Digital rectal examinations although relatively inexpensive are unpleasant and can be inaccurate. Fecal occult blood testing is nonspecific, colonoscopy and sigmoidoscopy are both uncomfortable for the patient and expensive. Double-contrast barium enema is also an expensive procedure. Because of the disadvantages of existing methods for detecting cancers, new methods are needed for cancer diagnosis. EXACT Sciences Corporation announced on February 4, 2009 that a United States has issued Patent No. 7,485,420 that covers the use of differentially methylated vimentin as a marker for the detection of colon cancer, based in part on applicants' discovery that the levels of vimentin transcript in tissues from human cancers are lower than the levels of vimentin transcript in normal tissues. Through its license agreement with Case Western Reserve University, EXACT has exclusive worldwide rights to the vimentin gene technology for non-invasive stool-based detection of colorectal cancer and pre-malignant colorectal polyps.

(EXACT Sciences Corporation, Feb 4, 2009)

Prostate Cancer

European Patent Office has issued Patent No. US2009087384 (A1) to Erguen Sueleyman [DE] et al, published on April 2, 2009 and entitled "Medicine and Method for Treatment of Prostate Cancer". The invention concerns a medicine for treatment of prostate cancer and a corresponding treatment method with which recovery chances are improved in the treatment of prostate cancer. The medicine can be supplied to a prostate tumor through the bloodstream, contains an active component and a binding component as well as ultrasound microbubbles. The binding component includes coupling molecules that specifically bind to a determined target molecule formed in the endothelium of tumor-associated blood vessels that is typical of the tumor or the tumor stage. The active component contains at least one chemotherapeutic substance. The coupling molecules are bound to the outside of the microbubbles and active substance molecules are likewise bound to the outside of the microbubbles or are enclosed by the microbubbles that can be destroyed (burst) by the application of an ultrasound field.

(European Patent Office, Apr 17, 2009)

GLOBE SCAN

HPV Testing Reduces Cancer Deaths

The remarkable promise of the Indian trial presents a worthy global challenge to implement smart, regionally tailored strategies that will efficiently save millions of lives in the years ahead. Led by Dr Rangaswamy Sankaranarayana of the International Agency for Research on Cancer , the randomized, controlled trial compared the efficacy of three methods of cervical cancer screening: visual inspection with acetic acid (VIA), pap testing (cytology) and HPV testing with QIAGEN's digene HPV test. Results from this milestone study, an eight-year trial conducted in Maharashtra state of India involving more than 130,000 women, demonstrated that in low-resource settings, a single round of HPV testing significantly reduced the numbers of advanced cervical cancers and deaths, compared with Pap testing or VIA. It is the first randomized controlled trial to measure incidence of cervical cancer and associated rates of death as the primary outcomes using different tools for screening. The implications of the findings of this trial are immediate and global; international experts in cervical-cancer prevention should now adapt HPV testing for widespread implementation . The study was supported with funding by the Bill & Melinda Gates Foundation.

*(*India: *QIAGEN NV, Apr 3, 2009)*

HPV-Positive Tonsil Cancer

According to a new Swedish study from Karolinska Institute that mainly covered the Swedish capital of Stockholm, the number of cases of tonsil cancer linked to the human papillomavirus (HPV), continues to increase with diagnoses tripling since 1970. Researchers found that since 1970, the cumulative incidence of HPV-positive, primarily as regards the virus type HPV16, tonsil cancer has increased from 23 to 93 percent, while the number of HPV-negative tumors has decreased. If the trend continues, almost all tonsil cancer in the Stockholm region will be HPV-positive, just as it is with cervical cancer for which 99.7 percent of cases are HPV-positive. In light of this new knowledge, researchers want to study different types of treatment impact on the diagnosis and side-effects for HPV-positive and HPV-negative patients. They also hope to discover the role of HPV vaccine in the oral cavity.

*(*Sweden: *Karolinska Institute, Apr 3, 2009)*

Test-Tube Model of Breast Cancer

An award-wining team of UK scientists at Queen Mary's University of London has developed a three-dimensional model of human breast cancer (ductal carcinoma in situ) in a test-tube which should help to reduce the number of animals used and improve the quality of cancer research. Scientists are constantly looking into ways to replace animals in medical experiments. This is an exciting development in both breast cancer research and the replacement of animals. The model is grown from donated human cells from both cancerous and healthy breast tissue and accurately replicates what happens in normal and malignant breast cells, containing all of the types of cells that are present in breast tissue. It is capable of being used for complex studies, including the identification and screening of new therapeutic targets and could replace experiments that currently require laboratory animals. The new model should also allow them to investigate the earlier stages and progression of the disease. This kind of technique is the way forward for breast cancer research.

*(*UK:*Cancer Research UK, Apr 1, 2009)*

Legislation to Improve Cancer Care

The Comprehensive Cancer Care Improvement Act, re-introduced on April 3, 2009, would improve care for millions of Americans diagnosed with cancer by empowering patients with written information necessary to make informed decisions - from the time of diagnosis and throughout their lives - and also by providing documented information that is crucial to coordinating care with other providers. Many cancer experts have concluded in a series of reports that the type of planning proposed in this bill will enhance the overall quality of cancer care by improving communication between doctors and patients coordinating active treatment and symptom management, promoting information sharing among healthcare practitioners, and ensuring appropriate follow-up care for survivors after primary treatment. This legislation is an important first step towards substantially improving cancer care in America. It is hoped that this bipartisan, common sense bill moves quickly through the legislative process and becomes a law. The bill has widespread support from cancer survivors, leading national patient advocacy organizations, physician groups and comprehensive cancer centers from around the country.

*(*US: *Medical News Today, Apr 3, 2009)*

CANCER CONTROL

Broccoli Sprouts

Broccoli has recently entered the public awareness as a preventive dietary agent. Three-day-old broccoli sprout eliminates Helicobacter pylori (H. pylori) infections –a widespread type of bacterial infection and a major cause of stomach cancer. The effect of broccoli in humans on the bacterial infection that leads to stomach cancer is explained for the first time in the study in which 70 grams of fresh broccoli sprouts or its equivalence in alfalfa sprouts were arbitrarily given daily to 48 Helicobacter-infected Japanese men and women for a period of eight weeks.

Using ordinary breath, serum and stool tests as methods of assessment, researchers evaluated the severity of H. pylori infection at enrolment. Eight weeks later, infection levels were noticeably lower on all three measures among those patients who had eaten broccoli sprouts, while they remained identical for patients who had eaten alfalfa sprouts. Due to the well established cause and effect link, a reduction in H. pylori probably leads to a decline in stomach cancer.

(Medical News Today, Apr 6, 2009)

Lymphedema

According to the National Cancer Institute, 25 to 30 percent of women who have breast cancer surgery with lymph node removal and radiation therapy, develop lymphedema. Breast cancer patients with lymphedema in their upper arm experienced reduced fluid in the swollen arm by up to 39 percent after undergoing a super-microsurgical technique, known as lymphaticovenular bypass, report researchers at The University of Texas M D Anderson Cancer Center. In lymphaticovenular by pass surgery, surgeons use tiny microsurgical tools to make two to three small incisions measuring an inch or less in the patient's arm. Lymphatic fluid is then redirected to microscopic vessels, approximately 0.3-0.8 millimeters in diameter, to promote drainage and alleviate lymphedema. The procedure is minimally invasive and is generally completed in less than four hours under general anesthesia, allowing patients to return home from the hospital within 24 hours. This procedure does a significant improvement in the severity of lymphedema.

(M.D. Anderson News, Mar 29, 2009)

RESEARCH DEPARTMENT ACTIVITIES

Retrospective Analysis of Lung Cancer Patients Treated at RGCI&RC, 2005-2007

Sheh Rawat, Ritesh Sharma*, R Ranga Rao**, Anamika Dwivedi*** & Pranav Chadha*.*

Material and methods: A retrospective analysis of 364 histopathologically proven lung cancer patients treated at Rajiv Gandhi Cancer Institute & Research Center (RGCI & RC) from 2005 – 2007 to find out the progression-free survival (PFS) and overall survival (OS) in the cohort and the factors influencing them.

Results: There were in total 296 male and 68 female patients with a median age of 59 years (range 23-92 years). 207 (56.9%) of the cohort had a history of smoking. The histopathological break-up was squamous cell in 81(22.7%) patients, adeno histology in 76 (20.9%), 33 (36.5%) had other non small cell lung carcinoma histology, and 69 (19%) had small cell histology. Stage-wise, 218 (60%) patients with stage IV were 40 (11%) being Stage IIIA and 65 (17.8%) being stage IIIB. Of the rest, 21 patients (5.7%) were Stage IA, 4 (1%) were stage IIA, 8 (2%) were stage IIB. Performance status (PS) wise, 182 patients (50%) were PS 0-1, 106 (27.5%) as PS-2, 58 (15.1%) as PS-3, and 28 (7.4%) as PS-4.

The time lag between development of symptoms and diagnosis was 3.7 months (95% CI 0.03-48.73). The time lag between diagnosis and commencement of treatment was 1.3 months (95% CI 0-22.47). A time lag between symptoms and diagnosis less than 1 month had a significant impact on both PFS and OS (p=0.018) and time lag between diagnosis and treatment less than 1.5 months had a significant impact on PFS and OS (p=0.028).

Conclusions: Inspite of being heterogenous data, early stage disease (stage I-IIA) had a significantly superior PFS compared to advanced stage disease (stage IIB-IV). The time lag between onset of symptoms and diagnosis, and time lag between diagnosis and treatment significantly impacted the PFS and OS and was an important predictor. In subset analysis of stage III, chemoradiation was found superior to chemotherapy alone in terms of OS but not PFS.

*(*Dept of Radiation Oncology; **Dept of Medical Oncology; and *** Dept of Research, RGCI & RC)*

RGCON - 2009: HIGHLIGHTS

Preamble

Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC) organized the 8th International Conference "RGCON-2009" from 27th-29th March 2009, with its main theme as ***"Thoracic Cancers: New Frontiers and Horizons"*** in pursuit of its efforts of Continuing Medical Education. The focus of the conference was on Lung and Esophageal Cancers. Dr (Col) R. Ranga Rao, Senior Consultant, Medical Oncology, RGCI&RC was the Organizing Secretary of RGCON-2009. The conference was inaugurated by the Chief Guest, His Excellency Dr APJ Abdul Kalam, former President of India. The event brought many experts of thoracic cancers on a single platform. As many as 100 faculties and 500 national and international delegates participated to share their expertise and the latest information on the scientific advances in thoracic cancers.

Lung and esophageal cancers are worldwide health problems in terms of incidence and mortality. Patients with these cancers often require complex therapeutic approaches that combine surgery, chemotherapy, radiation and, in many cases, novel therapies and procedures. Combating their causes, developing better methods for early detection and improving treatments, require the collaboration of many research and clinical specialties.

Inaugural Session

Presenting the inaugural address, Dr Kalam said that there was a need to spread awareness on cancer from the primary school itself. "Since 90% of lung cancer cases owe their origin to tobacco smoking, there is a need to accelerate the campaign against tobacco and alcohol consumption", said Dr Kalam. He also appreciated "Cancer News", a bimonthly publication of the Institute for widely disseminating the latest information on cancer.

A book entitled "Lung Cancer Update- 2009" was also released by Dr Kalam on the occasion. The book focuses on the significant recent developments in the field of lung cancer. The learned authors have presented an indepth understanding for their clinical applications in day- to-day practice.

To encourage high quality publications, the Institute confers the "Dr PS Raman Memorial Prize", an annual award, for the best paper published by clinicians/ researchers of the Institute, as adjudged by outside experts. For the year 2008, the Chief Guest presented this award to Dr Sudhir Rawal, Senior Consultant, Department of Surgical Oncology, RGCI&RC, for his paper entitled "Minilaparotomy Radical Cystoprostatectomy (Minilap RCP) in the Surgical Management of Urinary Bladder Carcinoma: Early Experience," published in the Japanese *Journal of Clinical Oncology*. The Chairman's Award for the Young Doctor of RGCI&RC for outstanding achievements was also presented by the Chief Guest to Dr Kirti Bhushan, who is presently working as a Clinical Assistant in Surgical Oncology.

Scientific Sessions

The scientific sessions comprised of Educational Sessions & Clinical Management Sessions. They were designed to highlight the latest advances in multimodal management for practicing oncologists and primary care physicians, with a special emphasis on early diagnosis in order to improve the cure rates. These sessions included orations, plenary sessions, symposia and panel discussions to afford interaction among the delegates. The scientific committee of RGCON-2009 also invited PG students/ researchers to submit papers/abstracts of their research work on lung and esophageal cancers. Around 30 abstracts were received and a prize each was given in the categories on prevention and investigations, including imaging, pathology, treatment & complications and interesting case reports.

A pre-conference Surgical & Endoscopic Workshop was held on 27th March 2009 at RGCI&RC. It consisted of live demonstration of surgical procedures and interventional bronchoscopy (Tracheobronchial Stenting, Electrocautery Laser, Medical Thoracoscopy, Endoscopic Ultrasound in Lung Cancer, Brachytherapy) and interventional endoscopy (Endotherapy of Barrett's Esophagus & Early Esophageal Cancers, Endoscopic Ultrasound in Esophageal Cancers) by renowned national and international faculty, like Dr Miguel A Cuesta, Dr JWA Oosterhuis, Dr Rajesh Mistry, Dr Harit Chaturvedi, Dr S Puntambekar, Dr Kapil Kumar, Dr A K Dewan, etc.

On the same day, a Merck Sereno Satellite Symposium on "Newer Strategies in the Management of Lung Cancer" was held at Hyatt Regency, Delhi. The symposium was chaired by Dr S H Advani, a Medical Oncologist of inteternational repute from Mumbai. Lectures on "Pharmacogenomics in Lung Cancer", "Cetuximab in Lung Cancer" and "Extending Survival

His Excellency, Dr. APJ Abdul Kalam, former President of India, being greeted by members of the Organizing Committee

Using Vaccine Strategy" were delivered by Prof Fortunato Ciardiello, Prof Purvish Parikh and Prof Charles Butts, respectively. The highly interactive presentations allowed for substantial exchange of ideas among the faculty and the audience.

The second day of the conference started with an Education Session on "Staging of Lung Cancer: Pitfalls". Other topics covered during the day were "Conventional Imaging in Lung Cancer- Scope & Limitations", "Impact of PET-CT in Staging of Lung Cancer", " Lung Cancer: Scenario in India", "Management of Early Stage Lung Cancer", "Management of Locally Advanced Lung Cancer", "Recurrent & Metastatic Lung Cancer" and "Current Options of Chemotherapeutic Agents in Lung Cancer". The Dr Raman Chadha Memorial Oration was delivered by Dr PM Shah of Gujarat Cancer Research Institute on "Pleural Effusion – Clinician's Dilemma".

The third day of this scientific feast started with dedicated Clinical Management Sessions on esophageal cancer. The topics covered were: "Early Esophageal Cancer: Management", "Role of Endoscopic Ultasonography in Esophageal Cancer", "Role of Minimal Invasive Surgery in Esophageal Cancer", "Locally Advanced Esophageal Cancer", and "Metastatic/ Recurrent Esophageal Cancer". Harish Chandra Bajoria Oration was delivered by Prof Miguel A Cuesta from the Netherlands, covering "Challenges and Controversies in Surgery of Esophageal Cancer". The session on "Targeted Therapy in Lung Cancer" was designed to provide cutting-edge information on the novel targeted anticancer therapies that are being developed, highlighting the mechanisms of action and the most current clinical data on those agents. The session also detailed the multiple signaling pathways that are disrupted in lung cancer as well as novel targeted approaches that specifically affect aberrant signaling in tumor cells.

Since survival in lung cancer patients is poor, quality of life is considered to be an important outcome in patients who develop this disease. A session on "Quality of Life in Lung Cancer," discussing all the related issues, was also covered during the conference. Primary Care Physicians play an important role in the early diagnosis of lung cancer. A panel discussion on "Workup of Cases and Management of Esophageal Cancer" was also arranged for the primary care physicians.

The medical researchers talked about the possibility of a cancer vaccine for lung that can stop the growth of the tumour. They said that it is not going to be a preventive vaccine like that available for smallpox, but it will help in stopping the growth of tumour.

Chief Guest Presenting the Best Paper Award to Dr Sudhir Rawal

The three-day event aimed at promoting scientific and practical medical education in the field of thoracic cancer. A vast majority of patients are diagnosed in advanced stages, where treatment does not prove to be as beneficial as it does in early stages. Therefore, there is a need to create awareness not just among the masses but among doctors as well.

This conference provided a comprehensive update and a multi-disciplinary perspective on diagnosis and treatment of lung and esophageal cancers, including results of translational research. It facilitated scientific and clinical exchange, with the aim of promoting an integrated approach to the management of these cancers, by bringing together authoritative national and international partners in thoracic oncology. It also gave an opportunity to all the participants to explore further understanding of epidemiology and biology of lung and esophageal cancers to ultimately contribute to enhancing its prevention and treatment.