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Ms Rupal Sinha *Research Officer*

Mr Saud Azam *Research Officer*

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From the Desk of Director Research

Cancer pain has been cited throughout the world as a seriously undertreated problem, having enormous consequence for the patients and their families. The Special Feature in this issue focuses on Winning Over Cancer Pain.

Flow Cytometry is at the forefront as a tool for the fundamental investigation into cancer. Perspective profiles this rapidly diversifying technology.

An Indo-German Seminar on "Ion Therapy: World Scenario and Need in India", a first of its kind in the country, was jointly organised by the Ministry of Science & Technology, Government of India, and RGCI & RC. Highlights of the Seminar have been reported in this issue.

The Institute has been granted Income Tax exemption under Section 35(I) (ii) of IT Act with effect from 01/04/2005. Donations provided to the Institute for scientific research would entitle the donor to 125% weighted deduction.

Pfizer Inc. is one of the world's largest research based pharmaceutical companies. Special thanks to Pfizer Products India for funding this issue of the Cancer News.

The Institute gratefully acknowledges the contributions made by Dr.A.K. Anand, Dr. (Col) R. Ranga Rao, Dr. S.L. Jain, Prof P.S. Negi, Dr. Dinesh Bhurani, Dr. Neeraj Jain, Dr. Pankaj Pande, Dr. Rakesh Agarwal, Dr. Rajat, Dr. Pankaj Agarwal, and Mr. A.G. Babu. Views and suggestions on Cancer News are welcome from the readers.

Dr. (Mrs.) Ira Ray

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This publication aims at disseminating information on pertinent developments in its specific field of coverage. The information published does not, therefore, imply endorsement of any product/process/producer or technology by RGCI&RC.

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SPECIAL FEATURE

WINNING OVER CANCER PAIN

Introduction

‘Pain is a more terrible load to mankind than death itself’ aptly applies to cancer pain. However, with good interventions, cancer pain relief is mostly achievable. Pain is a major symptom of cancer and occurs at all stages of the disease. In addition, pain is usually a hallmark of progression or metastatic spread in 65 to 85 percent of people with cancer when they develop advanced disease. In 10 to 20 percent of cancer cases, pain is difficult to treat, frustrating and poorly controlled. Currently, opioid pharmacotherapy is the principal weapon in the fight against cancer pain, but when less invasive treatments are unsuccessful, least invasive interventions are added to maximize pain relief. Interventional pain procedures target neural and non-neural pain generators. Neural blockade techniques provide excellent pain relief for neuropathic, sympathetic, nociceptive somatic or visceral pain. Neural blockade techniques are broadly categorized into non-neurolytic and neurolytic blocks.

Non-Neurolytic Blocks

Local anesthetic and corticosteroid blocks are used to treat a variety of pain syndromes. They can also predict how a patient will respond to neurolytic blocks. A good response to non-neurolytic interventions usually means the patient will benefit from neurolytic procedures as well. Fluoroscopic guidance improves the accuracy of these blocks and minimizes complications. Somatic, sympathetic and neuropathic pain respond to local

anesthetic injections or the continuous administration of anesthetic drugs through a catheter. Intercostal nerve blocks or interpleural analgesia are indicated in post-thoracotomy chest wall pain/intercostal neuralgia and radiculopathy requires selective nerve root blocks or transforaminal epidural injections when non-invasive treatments fail. Sympathetic blocks and other regional anesthetic techniques are employed in sympathetically maintained pain states, ischemic pain, posttherapeutic neuralgia and radiation plexopathy.

Neurolytic Blocks

Alcohol and phenol are the preferred agents for neurolytic procedures because they cause axonal degeneration within minutes and effectively interrupt the central transmission of pain impulses. Chemical neurolysis can result in immediate and total pain relief in selected patients with localized or regional pain. Opioid requirements decrease sharply, and patients on high doses of opioids will require careful tapering to avoid respiratory depression. Other indications for neurolysis are costopleural syndrome and sympathetically maintained pain in Pancoast’s syndrome. Unfortunately, potentially unacceptable side effects limit the utility of neurolytic blocks; but neurolytic blocks are still preferred over standard opioid analgesia to control intractable abdominal, pelvic and perineal pain.

The following four criteria must be met before a nerve block is considered appropriate: (a) Limited lifespan of three to six months; (b) A favorable risk-to-benefit ratio (i.e., the block will not impair bladder or bowel function or cause limb paralysis); (c) A poor response to primary antitumor treatment, which has not been able to reduce the tumor burden; (d) A good analgesic response and acceptable side effects with prognostic blocks.

Table: Autonomic Nerve Blocks

Neurolytic Block	Site/Condition Treated
Stellate ganglion	Head, Neck or arm pain
Gasserian ganglion	Trigeminal neuralgia and facial pain
Interpleural (thoracic sympathetic chain)	Upper-head, arms Middle-thorax, heart, lung Lower-abdominal organs, uterus, bladder
Celiac plexus (splanchnic nerves)	Pancreatitis, abdominal pain, visceral cancer pain
Lumbar sympathetic	Lower limb pain, retroperitoneal pain
Hypogastric plexus	Pelvic, perineal, urogenital pain
Sacrococcygeal ganglion (impar, Walther)	Rectal, urethral, perineal, vaginal pain

The neurolytic blocks have the following advantages in home care by relatives of patients, particularly in rural areas of India: (1) Neurolytic blocks provide longer duration of pain relief. (2) Drugs and inexpensive equipment required are readily available. Elaborate equipment is not mandatory. (3) Long-term indoor ward treatment is avoided, repeated visits to the urban pain center are not required. (4) Patient can remain at home, pain free even in rural areas where medical help is scarce.

Neurolytic Celiac Plexus Blocks (NCPB) and Splanchnic Nerve Blocks are routinely performed (and are preferred over standard analgesic therapies) for patients with intractable pain from pancreatic and upper gastrointestinal cancer. NCPBs provide immediate and substantial pain relief in 70 to 90 percent of cases, improve the patient's quality of life and significantly reduce opioid intake. The procedure can be repeated in three to six months, if the effect of the initial block wears off. NCPBs are performed percutaneously or intraoperatively. Under radiologic C-arm/CT guidance, 50 to 100 percent alcohol is instilled anterior to the aorta at the level of the L1 vertebral body. Injection site pain, diarrhea and temporary hypotension are transient adverse effects. A low complication rate is observed, since the risk of the neurolytic agent spreading to the somatic nerves supplying the lower limbs, bladder and bowel is minimal.

Superior Hypogastric Plexus Blocks (SHPB) are indicated for unrelenting pain from cancer of the pelvic viscera. This plexus lies in front of the L5 and S1 vertebrae in the prevertebral space. A spinal needle is placed percutaneously in this space from the back under radiologic guidance. Excellent analgesia is reported by 70 percent of patients after a SHPB. Reductions in pain scores and opioid consumption are reported to be significant, even in patients with advanced disease. No major complications have been reported following

SHPBs, although a potential risk exists for the spread of neurolytic agents to the nerve fibers controlling micturition, bowel motility and sexual function. The SHPB block can be repeated if pain recurs. Patients who fail two consecutive attempts are candidates for intraspinal opioid analgesia.

Ganglion Impar Neurolytic Blocks relieve perineal pain from cancer of the cervix, endometrium, bladder and rectum. The ganglion is a single, midline structure ventral to the sacrococcygeal junction and can be accessed by a midline trans-sacral approach.

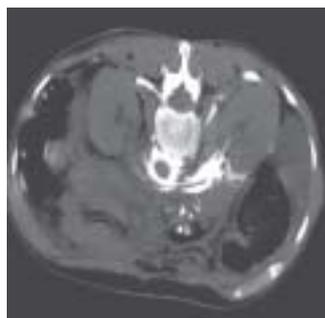
Painful input from somatic and visceral structures can produce sympathetically maintained pain (SMP) that may be visceral or neuropathic in nature. SMP is transmitted by a pair of paravertebral sympathetic nerve trunks that are easily accessible to blockade. *Sympathetic Ganglion Neurolysis* relieves SMP and improves blood flow and is used to treat pain from radiation plexopathy, phantom pain, herpes zoster, vascular insufficiency secondary to malignancy and complex regional pain syndromes (reflex sympathetic dystrophy and causalgia), with little risk of motor or sensory loss or deafferentation pain.

The *trigeminal nerve* receives sensory input from the skin of the face, anterior two-thirds of the tongue and oronasal mucosa. Anesthetic Blockade or Chemical Rhizolysis of the trigeminal ganglion or its individual branches is indicated in orofacial malignancies with intractable head and face pain. Complications include inadvertent dural puncture, neuritis and chronic corneal anesthesia.

Neurolytic Spinal Blockade can produce profound segmental analgesia. Nociceptive input is interrupted by selectively destroying the dorsal roots and rootlets between the spinal cord and the dorsal root ganglia. The procedure is reserved for terminally ill patients with



Celiac Plexus Block in CT-Guidance
Needle positions



Drug mixed with dye



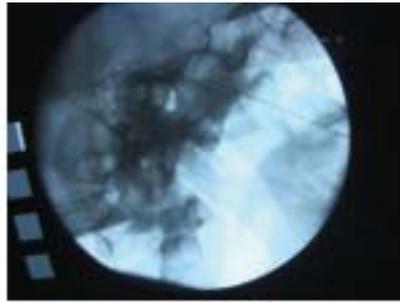
Superior Hypogastric
Block



Transsphenoid
Pituitary Chemoablation



Ganglion of Impar Block



Trigeminal Gangliolysis



Intrathecal Catheter Tunneled

cancer who have a short life expectancy and unilateral somatic pain localized to a few adjacent dermatomes, ideally in the trunk and distant from sphincter or limb innervation. Intraspinal tumors should not be present and the patient should respond well to prognostic local anesthetic blocks. *Subarachnoid alcohol/phenol blocks* effectively control pain in costopleural syndrome, which is caused by invasion of the pleural cavity and thoracic wall. Adverse effects include postdural puncture headaches, meningitis (rarely), persistent numbness and paresthesia, loss of motor function due to the unintended neurolysis of ventral rootlets and sphincter and limb weakness.

Trans-sphenoid Pituitary Neuroablation is also known as Chemical Hypophysectomy and is a very useful simple intervention with 70-80% success rate in diffuse cancers of advanced stage with multiple bony & spinal metastasis, especially hormone dependent cancers non responding to all other measures.

Intraspinal Opioid Therapy

Continued administration of opioids intrathecally or epidurally with or without dilute concentration of local anesthetic and adjuvant drugs is an important option for patients with thoracic, abdominal or pelvic cancer pain that is refractory to conventional pharmacologic management. Advantages include profound analgesia, often at a much lower opioid dose without the motor, sensory, or sympathetic block associated with intraspinal local anesthetic administration. However, combinations of low-dose opioids given epidurally with a local anesthetic act synergistically to produce effective analgesia while decreasing the side effects. Administration can be carried out using a variety of drug-delivery systems ranging from a temporary percutaneous epidural catheter to a totally implanted system. The effectiveness of preimplantation procedure and reversibility of effect makes this an attractive treatment option.

The drugs administered intraspinally for analgesia of cancer pain include:

- Opioid Agonists - Morphine, Hydromorphone, Fentanyl, Sufentanil, Merperidine, Methadone
- Alpha-2 Adrenergic Agonists - Clonidine
- Adenosine Agonists - Adenosine
- Acetylcholinesterase Inhibitors - Neostigmine, Physostigmine
- Calcium Channel Antagonists - Ziconotide
- GABA-Agonists - Baclofen, Midazolam
- NMDA-Antagonists - Ketamine
- Sodium Channel Antagonists - Bupivacaine, Tetracaine

Conclusion

Effectively relieving pain in cancer patients requires a range of treatment alternatives, including neural blockade when the patient's pain no longer responds to opioid analgesia. The type of neural block selected is determined by the location and mechanism of the pain, the physical status of the patient, the extent of tumor spread and the technical skill and experience of the person performing the intervention. Non-neurolytic blocks can provide safe and effective analgesia for the less serious conditions indicated above. Neurolytic blocks are reserved for patients who are unresponsive to standard analgesic pharmacotherapy and/or are at a more advanced stage of disease. However, few would question that aggressive intervention is often appropriate. Neurolytic nerve blocks offer an excellent option for the physician in the fight to control cancer pain. With proper training and experience, such blocks can be easily utilized to help provide cancer pain relief in most of cancer patients at the utmost needed times.

"Cancer pain is real and treatable, there is no merit in suffering."

(The Institute appreciates Dr. Neeraj Jain, Pain Specialist, for his contribution to this Special Feature on Winning Over Cancer Pain).

PERSPECTIVE

FLOW CYTOMETRY IN ONCOLOGY

Introduction

Over the past two decades, flow cytometry has become increasingly sophisticated. High speed sorters and analyzers capable of detecting a dozen colors and multi-parameters simultaneously have kept flow cytometry in the forefront as a tool for the fundamental investigation into cancer. Today, immunophenotyping by flow cytometry is an indispensable, powerful, rapid and cost effective tool for the diagnosis, classification, staging and monitoring of hematologic neoplasms.

Functional Components

A flow cytometer measures multiple properties of cells suspended in a moving fluid medium. As each particle passes in a single-file through a laser light source, it produces characteristic light patterns that are measured by multiple detectors for scattered light and fluorescent light. It can measure thousand of cells in a fraction of a minute.

Applications in Hematologic Malignancies

Acute Leukemias

Acute leukemias and lymphoblastic lymphomas can present with blast cells in peripheral blood, body fluids and bone marrow. Flow cytometric immunophenotyping can assist in the identification of these immature or abnormal cells, their discrimination from immature cells normally present in the bone marrow and thymus and determination of lineage in order to differentiate between Acute Myeloid Leukemia (AML) and Acute Lymphoid Leukemia (ALL) and assist to sub-type AML and ALL. Through the analysis of many thousand cells, flow cytometric studies can detect the precise percentage of blasts and the nature of blasts like T-cell lymphoblast, B-cell lymphoblast, Myeloblast, Monoblast, Plasma blast, Megakaryoblast and Erythroblast.

Chronic Lympho-proliferative Disorders

Mature B-cell lymphoid neoplasms: Flow cytometric immunophenotyping is indispensable for the diagnosis of mature B-cell lymphoid neoplasms through identification of phenotypically abnormal cells belonging to B-cell lineage and recognition of phenotypic characteristics of separate disease entities. Apart from the diagnosis, flow cytometry is frequently used to

identify target antigens for potential antibody therapy. Flow cytometry also provides prognostic information such as CD38 and ZAP-70 expressions in chronic lymphocytic leukemia.

Mature T- and NK-cell lymphoid neoplasms: Flow cytometric studies are one of the important tools in diagnosis and classification of mature T- and NK-cell lymphoid neoplasms. It also helps in the detection of potential targets for targeted therapy.

Plasma Cell Disorders

Flow cytometric immunophenotyping is a useful tool for the identification of abnormal plasma cells and distinguishing between lymphoid and plasma cell neoplasms. Besides, flow cytometry may provide additional prognostic information.

Myelodysplastic Syndromes (MDS)

Flow cytometric immunophenotyping may assist in the identification of MDS through identification of abnormal maturing myeloid cells, especially in the absence of significant morphologic dysplasia or increased blasts.

Detection of MRD

An improvement in flow cytometry has made it possible to detect Minimal Residual Disease (MRD) following therapy, especially in cases of ALL, AML and chronic lympho-proliferative disorders. Flow cytometric tests have now been developed to pick up one abnormal cell in 10,000 cells and in this respect it can compete with PCR based methods.

Solid Tumors

DNA content analysis in tumors was one of the earliest applications of flow cytometry. A large number of studies have attempted to define the prognostic significance of either ploidy or S phase fraction in a large number of different solid tumors.

Future Perspectives

Technologic advances in cancer diagnosis seem currently to focus on the methods of assessing genetic lesions in cancer. Although genetic abnormalities clearly produce cancer, they do so through production of abnormal proteins and detection of a number of different proteins in specific cell populations are what flow cytometry does best.

(The Institute appreciates Dr S.L. Jain for his contribution to the "Perspective" on 'Flow Cytometry in Oncology').

RESEARCH AND DEVELOPMENT

Breast Cancer Risk

BRCA genes were identified in the 1990s. Mutations in these genes are among the strongest known genetic risk factors for breast cancer. Researchers have identified new genetic variations in a region of DNA that might be associated with risk for breast cancer. Women with such variation have a 1:4 times greater risk of developing breast cancer compared to those without this variation. It is hoped that identifying the genes responsible for this increased risk may lead to new therapies that target the actions of these genes.

The researchers found that genetic variations in four single nucleotide polymorphisms located in a region of chromosome 6 were present more often in the breast cancer patients, suggesting that genes in this region might contribute to the risk of breast cancer. They also confirmed the finding of previous studies indicating that the locus named FGFR 2 is associated with a 20% increased risk of breast cancer. The variations in chromosome 6 that increase the risk for breast cancer were found in 23% of the women studied. They estimated that only about 7% of breast cancer cases in the current study could be attributed to the locus they found on chromosome 6.

(NCI News, Mar 3, 2008)

Cancer Treatment

Cancer cells have very high demands for purines, necessary for DNA replication and, ultimately, for cell replication. The ability to halt purine synthesis could prove to be a valuable method for treating cancer.

A group of Penn state scientists have observed for the first time in living cells a key step in the creation of purines. They used cervical cancer cells to demonstrate that a group of six enzymes are involved in the creation of purines and that these enzymes form a cluster prior to purine formation. They used fluorescence microscopy technology to study the enzyme clusters, in which, fluorescent proteins are attached to molecules of interest and viewed under a special microscope. If researchers could find a way to disrupt the formation of this particular enzyme cluster, it could become a potential new target for cancer therapy.

(Cancer Research News, Apr 4, 2008)

Drug Resistance in Childhood Leukemia

Researchers have successfully used laboratory studies of leukemia cells to explore the basis of resistance in other anti-leukemia drugs. However, such in-vitro tests have not worked with methotrexate. They analysed the genetic profile of St. Jude Children's Research Hospital's patients undergoing methotrexate treatment of ALL to identify genes that governed their response to the drug.

In this study of 161 ALL patients, the response to initial methotrexate treatment was measured and gene microarray analysed to measure the activity levels of 12,357 genes in the patients. They elected to focus on the 50 most highly significant genes among the large number of genes in treated patient that differed in their expression level at a very significant level. The gene expression patterns of patients who responded well to methotrexate when compared to those who responded poorly, they found distinct gene expression profiles among the groups. Some of these genes could become potential targets for developing other drugs that would make methotrexate more effective in those children who are resistant.

(St. Jude Children's Research Hosp., Apr 18, 2008)

New Lymphoma Therapies

Researchers from Herbert Irving Comprehensive Cancer Center of New York-Presbyterian Hospital and Columbia University Medical Center have developed effective new treatments for lymphomas. The complexity and variation of lymphoma types do not allow for a one-size-fits-all treatment approach. By increasing the number and quality of treatment options for lymphoma patients, their chances for survival could be improved. This is especially critical for patients who haven't responded to the standard therapies.

One of the most promising new therapies developed at the center is PDX (pralatrexate) for T-cell lymphoma. The drug is uniquely designed to camouflage itself as a folic acid, which allows it to be absorbed by the tumor, where it attacks the cancer. The therapy has been shown effective in 54 percent of patients who did not respond to the other treatments. Researchers are also exploring novel lymphoma treatments with drugs targeting Bcl-6 and an enzyme histone deacetylase has shown that drugs affecting these two targets will markedly synergize with the conventional chemotherapy and may lower the amount of chemotherapy necessary to achieve remission.

(Science Daily, Apr 28, 2008)

NEW TECHNOLOGIES

DIAGNOSTICS

Bladder Cancer Test

Researchers from the Medial University of South Carolina Foundation for Research and Development have announced a new diagnostic tool to detect and monitor bladder cancer by discovering new cell receptor on cancerous cells. When the receptor sloughs off the cancer cells, it could be found in the urine and prostate fluid (in men).

The receptor, the first of its kind, offers great potential as a non-invasive easy-to-make dipstick or rapid urine test that could transform the screening and diagnosis process for bladder cancer. The new diagnostic test could eliminate the need for invasive tests like cystoscopy and biopsies. The current tests have shown only 40% accuracy of diagnosis, while the new test has demonstrated 90% accuracy (100% specificity) in human urine samples of patients with various degrees of bladder cancer.

(Med. Univ. of South Carolina, Mar 11, 2008)

Real Time Screening

Researchers at the Stanford University School of Medicine have developed a new medical imaging technique to detect cancers in the body in real time. Using this technology, the doctors may one day be able to detect early stages of colon cancer without a biopsy, whereas, currently, colonoscopy is the best way of finding colon cancers.

In this study, the researchers found a short protein that sticks to colon cells in the early stages of cancer. They sprayed the protein attached to a fluorescent beacon into the colon which gloms on to any cancerous cells and creates an easily visible fluorescent patch. They then used a miniaturized microscope called CellVisio, to peer inside the colon. They saw fluorescent patches and could make out the individual cancerous cells that could become a useful research tool for studying the small number of cancer stem cells that are thought to establish the eventual tumor.

This technique could also be adapted to detect cancers in the mouth, esophagus and stomach.

(Science Daily, Mar 17, 2008)

EQUIPMENTS

Femtosecond Lasers

An ultra-fast, ultra-intense laser, or UUL, with laser pulse duration of one quadrillionth of a second, otherwise known as one femtosecond laser, could change cancer treatments, dentistry procedures, precision metal cutting and joint implant surgeries.

This laser has the unique capacity of interacting with its target without transferring heat to the area surrounding its mark. The intensity of the power gets the job done while the speed ensures that heat does not spread. Results are clean cuts, strong welds and precision destruction of very small targets, such as cancer cells, with no injury to surrounding materials. It is hoped that the laser would essentially eliminate the need for harmful chemical therapy used in cancer treatments. If laser kills cancer cells without even touching the surrounding healthy cells, that is a tremendous benefit to the patient. Basically, the patient leaves the clinic immediately after treatment with no side effects or damage.

(Medical News Today, Mar 14, 2008)

Mobetron for Breast Cancer Patients

The Mobetron is a mobile, self-shielding linear accelerator, has made groundbreaking radiation therapy technique a reality for the Japanese breast cancer patients. It delivers single dose intra-operative electron-beam radiation therapy (IOERT) to breast cancer patients, offering substantial physiological and psychological benefits to the breast cancer patients. Dr Veronesi from European Institute of Oncology, developed the single-dose approach for treating breast cancer which was adopted at Nagoya University Hospital, Japan.

Doctors deliver a single dose of radiation to patients during cancer surgery with Mobetron. This one treatment is equivalent to six weeks of post-operative radiation therapy. Thus, post surgery radiation therapy is eliminated. Radiation and surgical oncologists work in collaboration. Single dose IOERT results in substantially less dose to the healthy tissues and there is complete sparing of radiation to the skin. It reduces overall treatment time for the patient, resulting in a faster recovery and return to daily life. It also increases the chances for oncoplastic reconstruction at the time of lumpectomy. Ultimately, it would result in breast preservation of the patients with more convenience at less cost.

(Intra-Op Medical, Mar 11, 2008)

TREATMENTS

Levoleucovorin for Osteosarcoma

US Food and Drug Administration has given marketing approval to Spectrum Pharmaceutical's Levoleucovorin for injection. It is a novel folate analog formulation and pharmacologically active isomer of calcium leucovorin. It provides physicians and patients with an important treatment alternative to leucovorin. Levoleucovorin for injection is currently listed as a replacement for calcium leucovorin in the NCCN Clinical Practice Guidelines in Oncology.

Levoleucovorin injection is indicated after high dose methotrexate therapy in patients with osteosarcoma bone cancer, and to diminish the toxicity and counteract the effects of impaired methotrexate elimination or inadvertent overdose of folic acid antagonists. Levoleucovorin is the only commercially available formulation comprising only of the pharmacologically active enantiomer of leucovorin (levoleucovorin or (6S) – leucovorin). The company is planning to file for a supplemental New Drug Application with FDA for use in colorectal cancer in 5-fluorouracil containing regimens and an NDA amendment for an oral tablet formulation by mid-year 2008.

(Spectrum Pharmaceutical Inc., Mar 11, 2008)

New Treatment for Retinoblastoma

Retinoblastoma, a deadly inherited cancer, is the most common eye cancer in children and because there is no effective drug treatment, it is usually treated by removing the eye to avoid the cancer from spreading.

A new minimally invasive interventional radiology treatment successfully treats advanced retinoblastoma. This experimental treatment is being performed only at New York Presbyterian Hospital/Weill Cornell Medical Center and Memorial Sloan Kettering Cancer Centre. Using moving X-rays, an interventional radiologist threads a catheter up the femoral artery, guides it to the ophthalmic artery (feeding the eye and the tumor) and then injects a much larger, curative dose of the cancer-killing drug, Melphalan, while sparing the healthy tissues in the body. This new treatment allows many children to keep their eyes and in some cases-restores vision. It is especially important in bilateral retinoblastoma, where vision could be lost entirely.

(Medical News Today, Mar 18, 2008)

Targeted Therapy Cotara®

Cotara, an experimental treatment for brain cancer has shown promise, as per the Peregrine Pharmaceuticals, Inc. Cotara links a radioactive isotope to a targeted monoclonal antibody and has been granted orphan drug status and fast track designation for the treatment of glioblastoma multiforme and anaplastic astrocytoma by the US Food and Drug Administration.

This monoclonal antibody is designed to bind to a type of DNA that is exposed only on dead and dying cells. Cotara's targeting mechanism enables it to home in on these cells, delivering its radioactive "payload" directly to the center of the tumor mass and thereby destroying it "from the inside out" with minimal radiation exposure to the healthy tissues. Cotara is delivered using convection-enhanced delivery, which targets the specific tumor site in the brain. Early results of two Cotara clinical studies are considered a promising development in this deadly disease. In patients treated in the studies, Cotara appears to be safe and well tolerated, with no dose-limiting adverse events.

(Peregrine Pharma Inc., Mar 12, 2008)

Vandetanib (ZACTIMA®)

Vandetanib is AstraZeneca's investigational compound, being studied as a once-daily oral therapy that fights cancer by: inhibiting vascular endothelial growth factor receptor 2 which blocks the development of tumor blood supply; and inhibiting the epidermal growth factor receptor, which may lead to direct inhibition of cancer cell growth and survival. It also inhibits RET kinase activity which may be important to the growth and development of certain tumors.

Vandetanib is currently being investigated alone and in combination with chemotherapy treatments to determine its impact in treating a number of solid tumors. ZODIAC (ZACTIMA in combination with Docetaxel in non-small cell lung cancer) and ZEAL (ZACTIMA efficacy with Alimta in lung cancer) are part of a broad phase III clinical trial programme designed to gain an understanding of how vandetanib may benefit people with lung cancer. The other studies are ZEST (Vandetanib versus erlotinib) and ZEPHYR (Vandetanib + best supportive care (BSC) versus BSC). Vandetanib has also been awarded orphan drug status by the Food and Drug Administration.

(AstraZeneca News, Mar 13, 2008)

IN FOCUS

TELEMEDICINE

Introduction

Telemedicine refers to the use of communications and information technologies for the delivery of clinical care. It has the capability to bring the state-of-the-art healthcare to isolated areas, enabling the delivery of medical services to sites that are at a distance from the provider. Telemedicine may be as simple as two health professionals discussing a case over the telephone, or as complex as using satellite technology and video-conferencing equipment to conduct a real time consultation between medical specialists in two different countries.

Concepts

Real time (synchronous): It requires the presence of both parties at the same time and a communication link between them that allows a real-time interaction to take place. Video-conferencing technology is one of the most common technologies used in synchronous telemedicine. Peripheral devices which can be attached to the computer or the video-conferencing equipment can aid in interactive examination. This kind of consultation includes psychiatry, internal medicine, rehabilitation, cardiology, pediatrics, obstetrics and gynecology and neurology.

Store and forward (asynchronous): It involves acquiring medical data (like medical images, biosignals etc.) and then transmitting the data to the medical specialist at a convenient time for assessment offline. It does not require the presence of both parties at the same time. Common consultations include dermatology, radiology and pathology. Medical record, preferably in electronic form, should be a component of this transfer.

Applications

There has been great success with teleradiology, telepathology, telecardiology and teledermatology. Telemedicine encompasses different types of programmes and services provided for the patient.

Specialist referral services: These services involve a specialist assisting a general practitioner in rendering a diagnosis. This may involve a patient seeing a specialist over a live, remote consultation or the transmission of diagnostic images and/or video along with patient data to a specialist for viewing later. Radiology makes the greatest use of telemedicine. Telepathology in oncology

has been enhanced by the introduction of the “virtual slide”, an entire histologic section that is scanned into the computer. This permits the slide to be viewed on a computer monitor at any resolution that can be seen simultaneously at different places.

Patient consultations: Involves using audio, video and medical data between a patient and a primary care physician (or physician extender) for use in determining a diagnosis and treatment plan.

Patient monitoring: The most rapidly growing use of telemedicine is in home healthcare and hospice care. Home telemedicine is facilitated by patient monitoring services that use various devices to collect and send data to monitoring stations for interpretation.

Medical education: The earliest uses of telesurgery in surgical education were in transmitting of live surgery during conferences and then it quickly spread to providing courses, seminars and videos over the internet.

Advances in surgical oncology: Advances in technological applications in surgical oncology and telemedicine are coming together in robotic surgery, which, guided by a surgeon located miles away, has now become a reality.

Advantages

Telemedicine enables the delivery of medical services to sites that are at a distance from the provider and has potential to facilitate better communication between the patients and their providers. It also alerts doctors to medical emergencies and provides reminders when patients are due for cancer screening tests and other appropriate medical services. Routine follow-up visits by the patient can be limited to the peripheral clinic. Physician's visits from the tertiary hospital to the rural/peripheral centers can be cut down.

Disadvantages

Patient privacy is an area of concern when information is exchanged over the internet. Network and software security protocols consistent with national and state legal requirements should be provided. Prescriptions given over the internet can be misunderstood.

Limitations

Major limitations for telemedicine applications are in the areas of infrastructure, human resources, hospital systems, referral practices and illiteracy.

(The Institute appreciates Dr. Pankaj Pandey for his contribution to the feature 'In Focus' on Telemedicine.)

CANCER CONTROL

Antioxidants for Cancer

The study conducted by Rochester researchers has indicated for the first time that resveratrol, a natural antioxidant found in grape skin and red wine could help destroy pancreatic cancer cells by reaching to the cells' core energy source, or mitochondria, and crippling its function. The study is critical because, like the cell nucleus, the mitochondria contains its own DNA and has the ability to continuously supply cells with energy and stopping the energy flow theoretically stops cancer. This research indicates that resveratrol has a promising future as part of the treatment of cancer.

According to the study, the resveratrol concentration in red wine can be as high as 30 mg/ml and higher doses are expected to be safe as long as a physician is monitoring. Red wine consumption during chemotherapy or radiation treatment is not contraindicated. The researchers of the study said that perhaps, a better choice would be to drink as much red or purple grape juice as desired. Other well known antioxidants derived from natural sources include caffeine, melatonin, flavonoids, polyphenols, vitamins C and E.

(Biocompare News, Mar 25, 2008)

Choline Reduces Breast Cancer

Choline is an essential nutrient found in foods such as eggs. According to a new study conducted by researchers from University of North Carolina, egg choline reduces breast cancer risk by 24%. Choline is needed for the normal functioning of cells and increasing evidence shows that it may be particularly important for women, especially those of child-bearing age.

A study in 2003 found that eating one egg per day was associated with an 18% reduced risk of breast cancer whereas another study in 2005 reported that on eating at least six eggs per week, the risk of developing breast cancer was 44% lower than for those who ate two or less eggs per week. According to the Institute of Medicine, one egg contains 125.5 milligrams of choline, or roughly a quarter of the recommended daily supply, making eggs an excellent source of this essential nutrient. Top food sources of choline include egg's yolk, liver, wheat germ and cauliflower.

(The FASEB Journal, June 2008)

Colon Cancer Prevention

A study from the University of California marks a breakthrough in the effort to combat colon cancer. Using a combination of a targeted cancer-fighting agent called DFMO (difluoromethylornithine) and a low dose of a non-steroidal, anti-inflammatory drug, sulindac, have reduced the risk of recurring colorectal polyps, by as much as 95% with fewer toxic side effects.

DFMO is the basis of the drug eflornithine, which was initially developed as a cancer medication. Sulindac is used to treat arthritis and other inflammatory conditions. The researchers enrolled 375 patients (with a history of at least one colorectal polyp or adenoma) who were randomly assigned to either a combination of 500 mg of daily DFMO and 150 mg of sulindac or placebos. Patients were followed for three years. Results showed a 79% reduction in the overall risk for recurrent adenoma, 92% reduction in risk for recurrent advanced adenomas, 90% reduction in risk for adenomas >1 cm and a 95 % reduction in the rate of repeating adenoma among patients who had previously had more than one adenoma.

(Science Daily, Apr 16, 2008)

Mutation Database of Lung Cancer

First European Lung Cancer Conference has launched a groundbreaking free tool to help oncologists choose the best therapies for patients with non-small-cell lung cancer (NSCLC). The online database brings together data on all the known somatic mutations in a molecule called epithelial growth factor receptor (EGFR) which is known to correlate with response to tyrosine kinase (TK) inhibitors for lung cancer patients.

Researchers from Metropolitan Hospital, Athens, worked on the assumption that a comprehensive list of all somatic EGFR mutations coupled with data on the response of NSCLCs treated with TK inhibitors would help to determine whether a specific mutation was likely to correlate with clinical benefits. The database includes cumulative data from thousands of patients. Also, independent patient data for patients who have been treated with TK inhibitors and some who have not, is being added. A total of 12,244 patients are included, of whom 3,381 had somatic mutations in EGFR. The researchers catalogued 254 different mutations. The database offers a chance to improve treatment for people receiving TK inhibitors.

(Euro Soci for Med Onc, Apr 28, 2008)

GENOMICS

Chemoprevention

A large prospective lung cancer chemo prevention study provides the first systemic evidence that accessible tissue, the oral epithelium, can be used to monitor molecular events that take place in the lungs of chronic smokers.

The researchers examined the oral and lung lining tissue in chronic smokers to analyse the status of two crucial tumor suppressing genes, P16 and FHIT, known to be damaged or silenced very early in the process of cancer development. As these genes are silenced by methylation, so they compared patterns of methylation between oral and lung lining tissues. They observed strong correlation between methylation patterns in both tissues. Examining oral tissue lining the mouth to gauge cancer inducing molecular alterations in the lungs could spare patients and those at risk of lung cancer from more invasive, uncomfortable procedures used now. According to the researchers, not only lung cancer, but pancreatic, bladder and head and neck cancers, which also are associated with tobacco use, could be predicted.

(M.D. Anderson Cancer Center News, Apr 14, 2008)

Colon Cancer

Researchers at the University of Southern California have found that germline variations in the epidermal growth factor receptor (EGFR) DNA – a gene widely expressed in colonic tissue – is linked to the development of colon cancer and resulted in opposite survival outcomes for men and women. They expected to find that high expression would correlate with a poor prognosis and faster growth of the cancer. They found that men followed the expected trend, while women's response was the opposite.

Researchers analyzed 318 patients (117 men and 141 women) with metastatic colon cancer treated between 1992 and 2003 who were exposed to similar chemotherapy treatments. When genomic DNA samples were analyzed, researchers found that women who had specific gene variants linked with high expression of EGFR, had higher overall survival rate, while men with same variant had lower survival rates.

This is the first report to show that the prognostic value of EGFR depends on the gender. This may suggest

that, in the future, molecular markers should be evaluated differently in men and women and that treatment decisions may depend on the gender also.

(Univ of Southern California News, Apr 15, 2008)

Source of Mystery Cancers

Israel-based Rosetta Genomics has developed first microRNA based diagnostic tests that analyze genetic material, which can tell the doctors about the source of some mysterious cancers and perhaps help provide a short-cut for treating them. Mysterious cancers acquire the ability to metastasize so early in development that primary didn't develop or the primary never existed.

Researchers used microRNAs, a type of genetic material that regulates genes and known to be involved in cancer, as biomarkers to identify tumors that had spread in the body from unknown sources - a type of cancer known as 'cancer of unknown primary.' After examining 400 samples of 22 different tumor tissues and metastases, they identified the source in two-thirds of the cases and being able to identify the primary origin of a cancer is key to treating it. Results demonstrate the potential of microRNAs as effective biomarkers. It is a significant step towards the development of the first microRNA-based diagnostic tests.

(Reuters, Mar 23, 2008)

Window into Genetic Properties

Researchers at the University of California, San Diego School of Medicine, have shown that Magnetic Resonance Imaging (MRI) technology has the potential to non-invasively characterize tumors and determine which of them may be responsive to specific forms of treatment, based on their specific molecular properties. They have analysed more than 2000 genes that had previously been shown to have altered expression in Glioblastoma multiforme tumors. They then mapped the correlations between gene expression and MRI features. MRI could detect which part of a tumor expresses genes related to blood vessel formation and growth or tumor cell invasion, both of which are susceptible to treatment with specific drugs.

Understanding the genetic activity could prove to be a very strong predictor of survival in patients and help explain why some patients have better outcomes than others.

(The PNAS, Mar 24, 2008)

CLINICAL TRIALS

Experimental Drug for Osteosarcoma

Osteosarcoma is a rare cancer of the bone which typically affects children and young adults and no new therapies have been introduced in two decades. The largest final stage randomized trial in this disease of the experimental drug 'mifamurtide' along with chemotherapy showed that patients with osteosarcoma who received the drug fared better than patients who received chemotherapy alone. The trial included 662 patients with newly diagnosed non-metastatic osteosarcoma. After six years of follow up, overall survival was 78 percent in the group receiving mifamurtide plus chemotherapy compared with 70 percent in the group receiving chemotherapy alone. Addition of ifosphamide in the study did not enhance the event-free survival or overall survival for patients in the trial.

As an experimental agent, mifamurtide is available only through clinical trials. In 2006, IDM Pharma, manufacturer of mifamurtide, sought approval from the US FDA for its use in treating osteosarcoma. The FDA has requested more information and the company plans to submit new data showing an overall survival benefit in the disease.

(Journal of Clinical Oncology, Feb 1, 2008)

Stem Cell Transplantation

Investigators from the United Kingdom Medical Research Council and the Eastern Cooperative Oncology Group of the United States had jointly planned and performed the international acute lymphoblastic leukemia (ALL) trial from 1993 to 2006. Adult 1913 ALL patients were enrolled with or without a genetic mutation called the Philadelphia (Ph) chromosome. They compared the survival between the standard risk and high risk patients depending on their age, the number of white blood cells present at diagnosis and the presence or absence of the Ph-chromosome.

The result of the study showed that patients with standard risk, Ph chromosome-negative ALL lived significantly longer after chemotherapy-induced first remission when they received allogeneic (donor) stem cell transplantation instead of continued chemotherapy. Surprisingly, high-risk Ph-negative patients benefited less from having a stem-cell donor than the standard-risk patients. Autologous (self) stem cell transplantation was

less effective than continued chemotherapy for those patients without a stem cell donor. Thus sibling donor allogeneic transplant is the treatment of choice for adults with standard-risk ALL in remission, providing the greatest chance for a long-term survival.

(NCI-Clinical Trials Results, Jan 7, 2008)

Stomach Cancer Drug, S-I

A drug known as S-I is used as a first line treatment for stomach cancer in Japan. As yet, S-I is not approved for use in the United States. US doctors treat advanced stomach cancer with fluorouracil (5-FU). S-I contains tegafur, a substance that converts to 5-FU in the body. A potential advantage of S-I over the drug 5-FU is that S-I can be taken by mouth, whereas 5-FU must be given intravenously.

In a Japanese Phase III clinical trial, 298 patients with advanced, inoperable stomach cancer were assigned at random to treatment with either S-I alone or S-I plus cisplatin. Patients in this trial were followed for a median of almost three years. Those who received S-I plus cisplatin survived for a median of 13 months compared with 11 months for their counterparts who were treated with S-I alone. The combination therapy also delayed progression of disease for longer than S-I alone (six months vs four months).

(Lancet Oncology, Mar 2008)

Vaccine Cervarix®

GlaxoSmithKline's cervical cancer candidate vaccine Cervarix has been approved in 55 countries around the globe. Initial efficacy study of this vaccine was a double blind, controlled trial of 1,113 young women between 15-25 years of age, randomized to receive three doses of Cervarix for cervical cancer formulated with the AS04 adjuvant system or three doses of placebo on a 0, 1 and 6 month schedule. The extended follow up study looked at study endpoints for 776 women from the same cohort of women for a period of up to 76 months.

The new data demonstrated that Cervarix provides significant protection for women against the four most common cancer-causing human papilloma virus types for nearly six and a half years, the longest duration of protection reported to date. Over this time, Cervarix showed 100 percent efficacy in preventing precancerous lesions due to cancer-causing virus types 16 and 18, maintaining high levels of antibodies.

(GlaxoSmithKline, Mar 11, 2008)

WATCH-OUT

Cancer Immunotherapy

Hiserodt John C, Graf Martin R and Granger Gale R of the United States have been awarded a Patent No. US2008057029 entitled "Cancer immunotherapy using autologous tumor cells combined with cells expressing a membrane cytokine", published on March 6, 2008.

The invention comprises cellular vaccines and methods of using them in cancer immunotherapy, particularly in humans. The vaccines comprise a source of tumor-associated antigen and a cytokine-secreting cell line. Tumor antigen may be provided in the form of primary tumor cells, tumor cell lines or tumor extracts prepared from the subject. In certain embodiments of the invention, the cytokine-secreting line is a separate tumor line that is allogenic to the patient and genetically altered so as to produce a cytokine at an elevated level. Exemplary cytokines are IL-4, GM-CSF, IL-2, TNF-alpha and M-CSF in the secreted or membrane-bound form. In these, the cytokine-producing cells provide immuno-stimulation in trans to generate a specific immune response against the tumor antigen. Vaccines may be tailor-made by mixing tumor antigen with a favorable number of cytokine-producing cells or with a cocktail of such cells producing a plurality of cytokines at a favorable ratio.

(esp@cente.com, Mar 29, 2008)

Mammastatin Serum Assay

The University of Michigan was granted a pivotal patent on the core technology used in Abviva Inc's Mammastatin Serum Assay (MSA) to identify patients with breast cancer. MSA is a simple blood test that identifies and measures the amount of mammastatin in women. It was developed by the University of Michigan and licensed exclusively to Abviva, which also has the exclusive option to license the therapeutic uses of mammastatin to develop one or more breast cancer therapeutics.

Studies evaluating the test indicated that 98% of women who had never received a diagnosis of or treatment for breast cancer had normal or elevated levels of mammastatin, while 74% of women who had received a diagnosis of or treatment for breast cancer had either diminished or undetectable levels of mammastatin.

(Biocompare News, Feb 26, 2008)

Robotic Platform Imaging Technologies

Genetix Group Plc., the cancer diagnostic and biopharmaceutical technologies group, has been granted US Patent No. 7310147 covering a number of important features that include the integration of imaging capabilities into Genetix Robotic Platforms, most notably the ClonePix FL. It also provides intellectual property rights in the US market for robots with integrated optics for single and multiple wavelength excitation and spectroscopic analysis of cells and cell colonies.

The new patent covers the use of spectroscopic measurements, such as fluorescence to identify cells and colonies that produce biopharmaceutical proteins. In addition, the patent covers the use of various pin types to aspirate and pick cells and colonies identified upon the basis of the spectroscopic measurements. This patent covers a number of aspects of Genetix's technology within the field of cellular biology. These technologies enable to identify cell lines for therapeutic antibody production and identify and isolate stem cells. It is also complementary to Genetix's activities within the cell based diagnostic market.

(Genetix Group Plc, Mar 9, 2008)

Test for Gastrointestinal Tract Cancer

IST Superior Sanita (IT) has been assigned a patent (GB 2442059) entitled "Test for cancer of the gastrointestinal tract," published on March 26, 2008. The invention relates to testing for malignancy by assaying the presence of a cellular marker.

A test for malignancy in gastrointestinal (GI) tract tissue sample, comprises assaying the sample for the presence of the CD133 marker. The sample may be taken from the mouth, stomach, iliac, colorectal or preferably bowel cancer. The marker may be detected by microscopy, chromatography, fluorescence activated cellular selection or flow cytometry. Also claimed are: a method for establishing the presence of cancerous tissue in a GI tract sample comprising contacting the sample with an optionally labeled anti-CD133 antibody and establishing the level of antibody binding to the sample; a kit comprising said antibodies; a method of cultivating CD133+ GI tumor cells; a process for selecting therapeutic agents effective against cancers having CD133+ cells; a method of selecting treatment for cancer of the GI tract.

(European Patent Office, Apr 28, 2008)

GLOBE SCAN

Prostate Cancer Screening Programme

In Tyrol region of Austria, the expected number of deaths from prostate cancer more than halved after a programme was introduced to improve early detection and treatment of the disease. Nearly 87% of eligible men have been tested at least once since the programme was introduced in 1988. By 2005 cancer deaths had fallen by 54%, compared with 29% for the rest of Austria, which had not benefited from the programme.

Prostate specific antigen (PSA) testing was introduced in Tyrol in 1988 and since 1993, it has been freely available to all men aged 45-75 and men under 40 with a family history of the disease. The findings suggested that the combination of free PSA testing and free treatment for any resulting prostate cancer can lead to significant reduction in death rates. This free treatment normally involved surgical removal of the prostate. Before the programme was introduced, the prostate cancer death rates in Tyrol were similar to the rest of the country, but after the programme was launched, the death rate started falling by an average of 7.3% a year, more than twice the 3.2% observed in the rest of Austria.

(Austria: *Science Daily*, Apr 22, 2008)

Cervical Cancer Vaccination

Cervical Cancer Vaccination Scheme is being introduced in Scotland from September 1, 2008, a year before the rest of the United Kingdom. The scheme is designed to protect against two main types of cervical cancer causing human papilloma virus (HPV), strains 16 and 18. Girls aged 12 to 13 would be entitled to the vaccine. It would also be available to girls up to the age of 17 for three years as part of a 'Catchup' campaign to ensure as many girls as possible, receive protection. This is one of the biggest and most complex immunization programme ever undertaken in Scotland, and has the potential to deliver tremendous health benefits for future generations of young women, offering them protection against the virus responsible for almost three quarters of cervical cancers. It is hoped that the vaccine would reduce the number of women diagnosed with cervical cancer, with the lifetime risk of a woman developing the disease in Scotland currently standing at around one in 124.

(Scotland: *Cancer Research UK*, Apr 10, 2008)

Revolutionary Advances in Cancer Treatment

PhiloGene through collaboration with researchers in UK have found that a novel form of the cytokine VEGF, VEGFb, is an extremely potent anti-angiogenic drug. VEGFb™ is endogenously expressed and predominates in most of the normal tissues. Unlike conventional form of VEGF, VEGFb does not promote angiogenesis.

VEGFb appears to be much more potent and safer anti-angiogenic drug than the anti-angiogenic drug in market. The breakthrough discovery also provides the mechanism to explain why current anti-angiogenic drugs are significantly limited in both efficacy and safety. Current anti-angiogenic treatments are problematic, because they indiscriminately reduce the level of not only VEGF, but also VEGFb. The novel approach is specific and targeted: not to reduce quantitative VEGF expression per se in a tumor, but to re-establish the proper balance between pro and anti-angiogenic VEGF isoforms that exist in normal non-angiogenic tissues.

(UK: *Medical News Today*, Apr 29, 2008)

Cancer Treatments at Critical Pathway

Researchers from the University of Pennsylvania School of Medicine have discovered that the Notch signaling pathway, which determines the development of many cell types and is also implicated in some cancers, is not universally essential for the maintenance of stem cells. The findings indicate that inhibitors of Notch may not affect the bone marrow stem cells.

Notch is one of a select set of proteins that influence the development of a wide variety of types of cells. Prior work has shown that increase in signals generated by Notch are important in certain human tumors, particularly some kinds of childhood leukemia, making Notch an attractive target for new cancer therapies. However, it has also been suggested that Notch is needed to maintain the stem cells in the bone marrow from which normal blood cells are formed, raising the concern that Notch inhibitors might destroy the normal bone marrow. T-cell acute lymphoblastic leukemias, which make up about 15-20 percent of childhood leukemias can be stopped in the laboratory by new kinds of Notch pathway inhibitors. This new work showed definitively that adult bone marrow stem cells do not require Notch signals, indicating that it should be possible to give these inhibitors to the patients without fear of causing bone marrow failure.

(USA: *Univ of Penn. School of Med*, Apr 14, 2008)

ACTIVITIES OF RGCI&RC

CLINICAL BIOLOGY OF CANCER CERVIX

Dr. Kailash Narayan, MD, PhD, Head of Gyne Oncology at Peter MacCallum Cancer Centre, Melbourne, Australia, delivered a lecture on "Clinical Biology of Cancer Cervix – Implications for Designing Clinical Trials and Clinical Practices" on 19th April 2008 in the conference hall of the Institute. It was attended by Senior Consultants, Physicists, Resident Doctors and Research Officers in the Institute.

Dr N. R. Datta, Senior Consultant, Radiation Oncology, Rajiv Gandhi Cancer Institute & Research Centre, introduced Dr Kailash Narayan.

Cancer cervix treatment has evolved from surgery to radical chemoradiotherapy in advance stages. The common problem in radiation delivery was the late toxicity of urinary bladder and rectum.

Currently, with the advent of newer imaging modalities and radiation delivery techniques, there is an increase in understanding of radiation dosimetry and its utilization in external beam radiotherapy (EBRT) and intracavitary brachytherapy.

Dr Narayan explained the role of Magnetic Resonance Imaging (MRI) & Positron Emission Tomography (PET) scanning in the initial evaluation and diagnosis. Dr Narayan emphasized upon the limitations of the International Federation of Gynecology & Obstetrics (FIGO) staging system. He then discussed the treatment protocols followed at his centre in Australia, emphasizing the role of laparoscopic nodal staging before starting treatment in early stage cancers where surgery is an option. They follow two-stage surgery wherein the first stage is for nodal evaluation and in the second stage of radical hysterectomy is done after any nodal disease is ruled out. He discussed his ten-year experience in treating cancer cervix with chemoradiotherapy.

Dr Narayan treats his patients by conventional radiotherapy with concurrent chemotherapy in which the pelvis receives a dose of 40 Gy in 20 fractions. These doses are considerably lower as compared to doses followed worldwide. EBRT was followed by 4 to 5 sessions of biweekly intracavitary radiotherapy without any gap between external and intracavitary radiotherapy. Also intracavitary brachytherapy was delivered on outpatient basis. He opined that since he is achieving a good local control of about 85% with only 3/250 patients

having isolated pelvic failures at lower doses, he is able to avoid any serious rectal or bladder toxicity.

He discussed the limitations of point A based dosimetry in cervical intracavitary brachytherapy and emphasized upon conformal brachytherapy, using ultrasound for tandem position in uterus and dose prescription according to the disease measurements. The talk also covered the role of PET and MRI based radiation techniques.

Patterns of failure in his experience had mainly been nodal failures. Isolated pelvic failures were only three. He also showed a consistent failure rates of about 30% irrespective of treatment modality. Also, corpus involvement and nodal status were the predictors of failure rates.

ATTENTION

Clinical Study on Nasopharyngeal Carcinoma in Children and Young Adults

The information is directed to the physicians, pediatricians, surgeons and radiation oncologists coming with the first contact of the patients.

We are participating in an open label, randomized phase II study conducted globally, including India. Patient is currently randomized into two arms. In the control arm, they receive induction therapy containing a combination of cisplatin and 5-FU (CF). In the experimental arm, they receive induction therapy containing docetaxel in combination with cisplatin and 5-FU (TCF). After completing induction therapy, patients in both arms continue with consolidation chemo-radiation therapy.

Only children and young adults (more than 1 month old up to 21 years of age) with newly diagnosed Nasopharyngeal Carcinoma, stage IIB-IV and WHO histological type II or III, are considered for enrolment.

We would request you to send any eligible patients for evaluation and inclusion in the study. During the study, the expenses for the treatment and investigations will be borne by the sponsor.

We will be glad to answer any queries regarding the study. Please contact at the given numbers:

- 1) Dr (Col) R Ranga Rao – 9810297787/ 011-47022258; email- ranga_rr@vsnl.net
- 2) Dr Gauri Kapoor – 011-47022254
- 3) Dr Kopal Anil – 011-47022440; email- rarity2310@yahoo.co.in

BONE MARROW TRANSPLANT UNIT

Introduction

Since the establishment of a Transplant Unit 7 years ago, the Institute has carried out successful stem cell transplants within a very cost effective package, almost one-tenth of what it does in the west. When bone marrow (BM) transplantation was initiated for the first time in 1970, BM was used as a source of stem cells. However, now almost 60% of allogeneic transplants and 99% of autologous transplants are being done using peripheral blood stem cells. Cord Blood Transplants and Mismatched Allogeneic Stem Cell Transplants have also been performed successfully.

Hematopoietic stem cell transplantation is an effective treatment option for a wide range of malignant and nonmalignant disorders. Autologous stem cell transplantation (ASCT) refers to the hematopoietic reconstitution with the transplantation of the stem cells obtained from and to the individual harboring the disease, as against the reconstitution with the stem cells from a matched or unmatched donor in allogeneic transplantation. ASCT differs from allogeneic transplantation in one important respect: there is no graft-versus-host disease. However, the flip side of the same advantage is a lack of graft-versus-tumor effect in autotransplantation.

Stem cells harvest and storage is followed by high-dose chemotherapy that best hits the target malignancy or disease. In selected patients of solid cancers, such as breast cancer, or of hematologic cancers, such as Non Hodgkin lymphoma, high-dose chemotherapy (HDCT) has the potential of ablating all of the tumor tissues, visible or invisible. The natural fallout of HDCT is complete ablation of the stem-cell reserve in the bone marrow. ASCT in these cases is performed as a "rescue," with the intention to repopulate the marrow with the stem cells till the hematopoietic reconstitution occurs.

BMT Unit

BMT unit of the Institute is located on the 3rd floor, B Block of the hospital and is segregated from other wards to ensure disinfection. It has four rooms, each with a single bed provided with double glass door. The main room has a single bed, bedside lockers, nurse-calling system, central oxygen supply and IV stand. The room also has Pulse Oxymeter, TV facility and telephone facility. Each unit has an ancillary hand washing area

where the doctor, nurse and the relatives are compulsorily required to scrub before entering the patient's room. The unit has laminar air flow systems which ensure thorough air conditioning. All the antiseptic conditions and precautions are maintained in the unit. The reception has close circuit monitors where the patient's condition can be monitored regularly. The patient is admitted in the unit for 20-25 days.

Stem Cell Harvesting

Stem cells may be harvested from bone marrow or peripheral blood. Peripheral Stem Cell Harvest (PSCH) is a process used to extract the stem cell from the blood stream. There is evidence to suggest that harvesting from the peripheral blood, as compared with that from the bone marrow, yields better results in terms of time to neutrophils and platelet recovery (i.e. hematopoietic reconstitution). Harvesting starts with the stimulation of growth of the stem cells with filgrastim (G-CSF). A rise in total leucocyte count not accounted for by infection or other causes is a surrogate indicator of high peripheral-blood stem cells numbers. Stem cell apheresis is performed after processing several litres of blood in the machine in 2 to 5 sessions in 2 to 5 days. Stem cells harvested are stored with DMSO (Dimethyl Sulfoxane) and liquid nitrogen at a temperature of -173 degree Celsius.

Procedure of Transplantation

Preparative regimens chosen depend upon the target disease. The objective of myeloablative preparation before transplant is to eradicate cancer and in allogeneic transplant to induce the immunosuppression that permits engraftment. The preparative regimens can be with or without Total Body Irradiation (TBI). After the preparative chemotherapy and/or the TBI, infusion of the thawed stem cells is performed. For the facilitation of harvesting, actual "transplantation" and later supportive care, it is imperative to have a credible venous access. A central venous access in the form of Hickman's double lumen catheter is ensured.

Care of the Transplant Patient

Until the marrow reconstitution occurs, extreme care is required. The main determinant of a successful transplant is the quality of supportive care. Febrile neutropenia is treated aggressively. Occult infections are identified early and dealt with the appropriate antibiotics. Fungal infections need to be identified and managed emergently.

INDO-GERMAN SEMINAR

ION THERAPY

“Indo-German Seminar on Ion Therapy: World Scenario and Need in India” was jointly organized by the Ministry of Science & Technology, Government of India and Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC), New Delhi on 14th and 15th April 2008 at India International Centre, New Delhi. The seminar provided the required forum for Indian and German experts in carbon ion and proton beams based on cyclotron/synchrotron facilities for use in radiation oncology and medical physics.

Radiotherapy for the future lies in proton and ion beam based intensity modulated particle therapy as against the present photon based Intensity Modulated or Image Guided Radiotherapy techniques. Ion therapy holds a great promise to treat many types of cancers more effectively, which could not be managed earlier. Carbon Ion Therapy is the preferred modality for resistant tumors and tumors in and around critical areas like eyes, brain and spine, especially unresectable retro-peritoneal soft tissue sarcomas, osteosarcomas, chondrosarcomas and chordomas of skull base, melanoma and adenocystic carcinoma, malignant salivary gland tumors, and lung and pancreatic cancers.

Keeping in view this new branch of radiation, the seminar mainly focused on the relevant issues and experiences at an international platform. Around 50 delegates from India and Germany participated and shared their expertise on the new technology. The German experts included specialists from GSI, Darmstadt, Germany and representatives from Siemens.

The seminar commenced with a backdrop of the seminar delivered by Mr Y P Kumar, Advisor and Head International Division, Department of Science & Technology, Govt of India. Dr Heinz Wirth, Germany of the Embassy of Germany in Delhi gave his observations on behalf of the embassy. Dr G. Kraft, GSI, Germany, and one of the key persons in developing this technology, gave an outline of ion therapy developments at GSI, Germany. Dr Gunzert Marx from Siemens, Germany, gave an insight of the facilities and equipments in cancer treatment available in Germany. An overview of the strategic alliances between India and Germany in this regard was presented by

Dr K. V. Swaminathan, Chairman, RGCI&RC. Dr T. Ramasami, Secretary, Ministry of Science & Technology, Govt of India, delivered the inaugural address and covered developments in science and technology with reference to saving life.

The introductory session was chaired by Prof Dr G.K. Rath from AIIMS and Dr K. V. Swaminathan. It commenced with a lecture on “Rational and Technology of Ion Beam Therapy” by Dr Kraft. He mainly explained that particle therapy with protons and heavier ion beams offered physical and, in case of carbon ions, biologic advantages over photon radiotherapy. Particle therapy, however, is more complex and cost intensive and focused quality assurance is needed for clinical use.

The next session on “Hadron Therapy Facilities: Basics and Market Overview” was chaired by Dr R.K. Bhandari and Dr N.R. Datta. In this session, the first talk was on “Review of Development in Using Nuclear Particles in Radiation Treatment of Cancer” by Dr M.R. Raju, Mahatma Gandhi Memorial Medical Trust, Andhra Pradesh, India, who had spent most of his career in the research of pions and hadron therapy; he gave a historical review of this technology. The second talk was on “Clinical Ion Beam Facility – Global Perspective” by Dr L. Filipsson, Siemens Particle Therapy, Germany. He gave the worldwide installation and overall view of this technology with respect to the geographic context.

The next session on “Infrastructure and Financial Aspects” was chaired by Dr V.S. Ramamurthy and Mr Y. P. Kumar in which Dr R. K. Bhandari of Variable Energy Cyclotron Center, Kolkata, gave the lecture on 'Technical Support Potential in India and Asia.' He also discussed the scientific and technical facilities of cyclotron facility for therapeutic energy range. Dr Amit Roy from Inter-University Accelerator Center, Delhi, discussed about the infrastructure in Delhi to promote this technology. Dr Filipsson then discussed the 'Economical Aspects of a Particle Therapy Facility' which included business plan, reimbursement, market risk etc. He pointed out the long term running of this facility on the basis of economical review. The next talk on “Cost of Radiotherapy with New Technologies” was delivered by Dr Rakesh Jalali, Tata Memorial Hospital, Mumbai, who highlighted the technical feasibility issues fully on the basis of Indian clinical environment. He stressed on the type of Indian cancers suitable to be best treated by ion therapy and the status of its present day management in India.



The session on "Particle Therapy" was chaired by Prof P.S. Negi, Organizing Secretary of the seminar and Dr P.K. Julka. Dr Hartmut Eickoff, GSI, Germany, delivered a lecture on "Heidelberg Ion Therapy Center - Proton Ion Accelerator Facility - From Design to Commissioning." He broadly discussed the room design and parts of the technology in detail. His practical knowledge in implementing the technology was well accepted by the audience. Dr Marx then delivered lectures on "Siemens Particle Therapy Solution - A Workflow Driven, Particle Therapy Facility (Technique, Workflow, Medical Equipment, Layout etc)" and "Result of Proton and Carbon Ion Treatments". Her lecture broadly covered the queries of both technical and clinical communities. The last session was chaired by Dr R. Sarin and Dr S. Hukku. Dr. A.K. Anand, RGC&RC, Delhi delivered a lecture on "Long Term Result and Morbidity Reviews." He discussed, on the basis of the literature available, the comparisons between present radiotherapy techniques and ion therapy facilities.

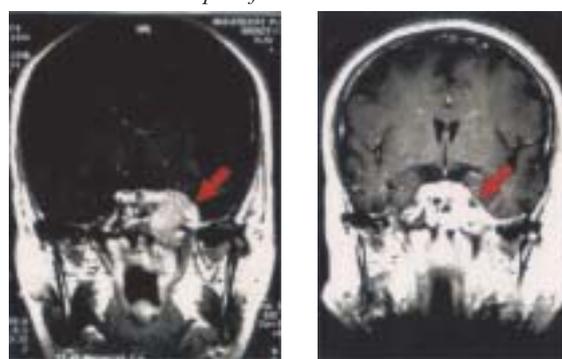
The first day of the seminar ended with a panel discussion among Dr H. Gutbrod and Dr Kraft from Germany and Dr Rajiv Sarin, Director, ACTREC (TMH) and Dr R.K. Grover from India. A lot of basic and interesting questions were answered and discussed in the panel moderated by Prof Negi.

On April 15th, the first session started with a lecture by Prof Kraft on "Radiobiology of Ion Therapy- Experiment and Modeling." It covered the modeling of proton and heavy ion beam treatment planning, its radiobiological consequences, the practical treatment planning and the theory behind it, especially Relative Biological Effectiveness (RBE) of proton and carbon ion beam. The next lecture was on "Therapy Planning for Protons and Carbon Ion" by Dr Marx, who explained the actual treatment planning parameters and the tools to achieve a good plan.

The seminar was reviewed by Mr Kumar and Dr Swaminathan with inputs from the Indian and German experts and the participants. The discussion was mainly on the clinical implementation of high energy protons and ion therapy fueled by the combination of the apparent advantage of dose distribution, early clinical results and equipments.

The last lecture was by Dr S.P. Agarwal, Atomic Energy Regulatory Board, Mumbai, on "Regulatory Issue in India". He explained the present regulatory rules and acts for radiation protection and need to formulate the rules for these new radiotherapy beams.

Example of a Treated Patient



Before RT

Six weeks after RT

The participants were sensitized that many proton and ion therapy centres are operational across the world and have treated a variety of cancers in USA [Loma Linda University Medical Center, Massachusetts General Hospital (MGH), LBL]; Europe [Paul Scherrer Institute (PSI), Switzerland; Gesellschaft für Schwerionenforschung (GSI), Darmstadt, Germany; Centro Nazionale di Adroterapia Oncologica (CNAO) and HIT etc.]; Japan [National Institute of Radiological Sciences (NIRS) etc.], China and South Africa. Proton and ion beam therapy facilities are also being established in the clinical setup in Germany, Switzerland, Italy, Japan and Korea. Ion therapy has become a reality and such centres in India could be a blessing for the cancer patients of India and neighbouring countries. The seminar ended with a vote of thanks by Mr Kumar and Prof Negi.

An Executive Committee meeting was held after the seminar. It was attended by Dr Gutbrod, Dr Kraft, Mr Kumar, Dr Bhandari, Dr Agarwal, Dr Grover, Dr Anand, Mr Ragavan and Prof Negi. A roadmap was discussed to bring carbon ion/proton therapy facility in India. The deliberations concluded that a public-cum-private consortium is the need of the hour to derive benefits of this technology for the Indian cancer patients.