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From the Desk of Director Research

The "Special Feature" in this issue highlights 'Triple Negative Breast Cancer' which carries poor prognosis due to aggressive biology and resistance to presently available hormonal and targeted therapies. Finding tailored treatment regimens for this subgroup of breast cancer remains a challenge. 'Transarterial Chemoembolization of Hepatocellular Carcinoma' profiled under "Perspective" has been widely accepted as standard therapy that can benefit, hepatocellular carcinoma patients ineligible for curative treatment, in terms of survival, whereas "In Focus" details 'India's Superconducting Cyclotron', a high tech accelerator for treatment of cancer using proton beams.

Cancer of the cervix takes heavy toll on the lives of women. To lay emphasis on prevention and early detection, November 2009 was observed as Cervical Cancer Awareness Month in Rajiv Gandhi Cancer Institute & Research Center; it has been portrayed under 'Cervical Cancer Awareness'. Dr Mahesh Mansukhani, Associate Professor of Clinical Pathology, Columbia University, USA, delivered a lecture on 'microRNA-Upcoming Significance in Cancer Diagnostics'. A 'Workshop on Uro-Oncology' was organized by the Institute and a new 'Gamma Camera' has also been installed. All these events have been covered under "Activities of RGCI&RC".

'Placement of Y-Shaped Stent for Malignant Tracheal Stricture' performed for the first time in India by a multi-disciplinary team of pulmonologists of the Institute has been summarised under "Case Report of RGCI&RC".

We gratefully acknowledge the contributions made by the Clinicians, Scientists and DNB candidates of the Institute.

Views and suggestions from the readers are welcome.

Dr D C Doval

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SPECIAL FEATURE

TRIPLE NEGATIVE BREAST CANCER

Introduction

Breast cancer is a heterogeneous disease. It encompasses several distinct biological entities that are associated with specific morphological and immunohistochemical features and clinical behavior. For many decades, invasive breast carcinomas were classified according to histological type, grade and expression of hormone receptors [estrogen receptor (ER) and progesterone receptor (PR)]. Recent microarray expression profiling analyses has demonstrated that breast cancers can be systematically characterized into biologically and clinically meaningful five main sub-groups, two of them ER positive (luminal A and B) and three ER negative [normal breast like, human epidermal growth factor receptor2 (HER2) and basal-like]. Breast cancers lacking the expression of ER, PR and HER2 receptors are called Triple-Negative Breast Cancers (TNBCs).

TNBCs comprise approximately 15-20% of breast cancer cases. These are highly proliferative, faster growing and more sensitive to chemotherapy drugs that affect the dividing cancer cells. They carry poor prognosis due to aggressive biology and resistance to presently available endocrine therapies, agents targeting HER2 pathways and in some cases, standard cytotoxic chemotherapeutic agents.

Basal-Like Breast Cancers and TNBCs

The terms TNBCs and basal-like breast cancers are often used interchangeably by clinicians. Although both share numerous clinical and pathological features, yet are not identical. Triple negative (TN) is an immuno-histochemical definition and basal-like stems from gene expression profiling. Basal-like breast carcinoma is characterized by certain gene expression clusters expressed in normal basal/myoepithelial cells of the breast, high-molecular-weight 'basal' cytokeratins (CK: CK5/6, CK14 and CK17), vimentin, P-cadherin, c-Kit, Ü B crystallin, fascin and caveolins. They frequently lack expression of hormone receptors and HER2, show either P53 immunochemical expression or TP53 gene mutations and express epidermal growth factor receptor (EGFR) in more than 60% of cases.

Not all basal-like cancers defined by gene expression analysis are TN, nor all TN tumors are basal-like. In the majority of cases, however, these two categories share similar clinical features, prognosis and treatment options. For this reason, terms TNBC and basal-like tumor are used interchangeably.

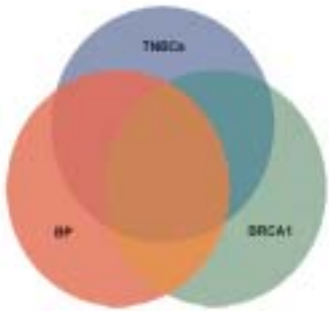


Figure: *Inter-relationship among Triple negative breast cancer (TNBCs), Basal phenotype (BP) and BRCA1*

BRCA1 and TNBCs

TNBCs and breast cancers in carriers of the BRCA1 mutation bear significant resemblance in terms of phenotypic and molecular features. BRCA1 mutation carriers tend to have basal-like subtype tumors. The similarities between basal-like breast cancer and BRCA1 associated TNBCs indicate that basal-like breast cancers may possess functional defect in BRCA1 and its repair mechanism via aberrations in the BRCA1 gene.

Clinical Characteristics and Patterns of Recurrence

The main characteristics of TNBCs include the fact that they more frequently affect younger patients (<50 years), more prevalent in African-American women, often present as interval cancers (e.g., cancer arising between annual mammograms) and are significantly more aggressive than the tumor pertaining to other molecular subtypes. A distinctive difference between recurrence patterns of TNBC and other forms of breast cancer has been noted. The pattern in TN is characterized by a rapidly rising rate in the first 2 years, with a peak at 2–3 years after diagnosis, then the risk of recurrence subsequently declines over the next 5 years. The majority of patients who did not have recurrence of disease after 8 years did not relapse afterwards, whereas in other forms of breast cancer, the risk of recurrence keeps rising as time progresses. Not only was timing of recurrence different, but TNBCs also had a significantly higher proportion of distant recurrences, only rarely

preceded by local recurrence. Pattern of metastatic spread of tumors was less likely to axillary nodes and bone and more of haematogenous spread with a peculiar proclivity to develop metastatic deposits in the brain and lungs. No correlation between tumor size and presence of lymph node metastasis has been observed in the TNBC group. Patients have a significantly shorter survival following the first metastatic event when compared with those with non TNBC controls.

Diagnostic Features

TNBCs most commonly present as a circumscribed mass without associated micro calcifications. This lack of calcifications is reflected at a histological level by a low incidence of associated ductal carcinoma in situ. Hence, mammography may not be the ideal tool for early detection of TN cancers. Magnetic resonance imaging (MRI) features are mass-type lesions dominated by their ductal phenotype with typical malignant enhancement kinetics on MRI. A higher fluorodeoxy glucose uptake was found in the TN group on Positron emission tomography scan with sensitivity of upto 100%.

Pathological Features

Majority of TNBCs are ductal in origin, other aggressive phenotypes appear to be overpresented, including metaplastic, medullary and adenoid cystic. They are usually of high histological grade. Morphological features include pushing border of invasion, lymphocytic response, high nuclear grade, high mitotic count, high nuclear cytoplasmic ratio, spindled tumor cells, metaplastic features and geographical tumor necrosis.

Current Treatment and Prognosis

The great interest in TNBC is not surprising, given that previous studies have shown that these cancers benefit neither from hormonal therapies nor from treatments targeted against HER2 receptors. The only systemic therapy currently available is chemotherapy, and prognosis remains poor.

At present, there are no recommendations for specific treatment regimens to be used in TN cancers and their subgroups. TN cancer is not associated with increased risk for locoregional relapse after conservative surgery. Data does suggest that combination therapy may offer improved outcomes in terms of progression free survival (PFS). TNBCs are sensitive to chemotherapy and have exhibited a greater likelihood of complete response to neoadjuvant therapy. Complete response rates are doubled in the TN subgroup compared with the remaining cancers. They may respond better to chemotherapy because of their high index of proliferation, indicated by high expression of Ki-67. Patients who fail to achieve complete response tend to relapse earlier and subsequently have poor outcomes. Anthracycline and taxane based regimens have traditionally been used in breast cancer patients, including TNBC patients, with evidence of antitumor activity and improvement in clinical outcomes. A recent study of vinorelbine plus gemcitabine vs vinorelbine alone demonstrated a significantly prolonged PFS with the combination regimen. Epothilones, a novel class of microtubule stabilizing agents, are less susceptible to cellular mechanisms of resistance and Ixabepilone, the most advanced drug in clinical development, in combination with capacetabine in metastatic TNBC has shown three-fold increase in response rates with 32% reduction in risk of progressive disease and 2 months improvement in PFS compared to capacetabine alone. This drug has received FDA approval for treatment of metastatic or locally advanced breast cancer after failure of anthracycline and taxane and is under evaluation in the neoadjuvant as well as first line setting

Future Prospects

Tageting DNA Repair Complex

BRCA1 mutation and subsequent defect in DNA pathway is potentially associated with decreased anthracycline sensitivity and increased platinum sensitivity, particularly to cisplatin. TNBCs with BRCA1 mutation show an exquisite sensitivity to inhibitors of the poly ADP-ribose polymerase (PARP) enzyme which is essential for repair of single-stranded breaks and BRCA1 function. A phase II study with the investigational PARP-1 inhibitor BSI-201, in combination with standard gemcitabine and carboplatin chemotherapy, presented during plenary session at the ASCO's annual meeting on May 31, 2009 showed significantly better outcomes in metastatic TNBC patients compared to women who received standard chemotherapy alone. BSI-201 developed by Sanofi-Aventis is now undergoing phase III trial. Other agents that cause DNA breaks, including etoposide and irinotecan, may also share selective activity in TNBCs with BRCA1 mutations.

Targeting Other Molecular Pathways

EGFR inhibitors alone have not exhibited promising antitumor activity in breast cancer, but they may enhance

Table: Ongoing Trials - Triple Negative Breast Cancer

Clinical Trial	Sponsors / Collaborators	Intervention	Phase	Start / Completion
A Study of Dasatinib (BMS-354825) in Patients With Advanced "Triple Negative" Breast Cancer	Bristol-Myers Squibb	Dasatinib	II	December 2006 Completed
Platinum for Triple Negative Metastatic Breast Cancer and Evaluation of p63/p73 as a Biomarker of Response	Massachusetts General Hospital Beth Israel Deaconess Med. Cen. Dana-Farber Cance Institute North Shore Medical Center	Drug: Cisplatin Drug: Carboplatin	II	June 2007/June 2010 Recruiting
Cetuximab and Cisplatin in the Treatment of "Triple Negative" Metastatic Breast Cancer (BALI - 1)	Merck	KGaA Cetuximab Cisplatin	II	June 2007/March 2009
Bevacizumab and Abraxane as Second-Line Therapy in Triple Negative Metastatic Breast Cancer	University of Pennsylvania Genentech	Bevacizumab Abraxane	II	May 2007/Dec 2011 Recruiting
Gemcitabine and Cisplatin as First- Line Combination Therapy in Patients with Triple Negative MBC	Fudan University	Drug: Gemcitabine Cisplatin	II	Sept 2007/Sept 2009 Recruiting
A Randomized Trial of Ixempra Versus Taxol in Adjuvant Therapy of Triple Negative Breast Cancer (TITAN)	Sarah Cannon Research Institute SCRI Oncology Research Consortium Bristol-Myers Squibb	Drug: Doxorubicin Drug: Cyclophosphamide Drug: Ixabepilone (Ixempra) Drug: Paclitaxel (Taxol)	III	Jan 2009/Jan 2016 Recruiting

the effect of chemotherapy in TNBCs. Clinical trials testing the efficacy of humanized anti-EGFR monoclonal antibodies and EGFR tyrosine kinase inhibitors (TKIs) are currently underway in patients with TNBCs. c-Kit has been shown to be preferentially expressed in tumors lacking hormone receptors and HER2 expression. Imatinib mesylate is c-Kit inhibitor that could be used as a tailored therapy for TNBCs.

Dasatinib, a src pathway inhibitor, has been shown in preclinical studies to be effective in breast cancer cell lines with a TN phenotype. Patients who responded to this TKI had cancers preferentially lacking ER, PR and HER2 and expressing CK5 and CK17. It has been demonstrated that caveolins 1 and 2, which are substrates for src family kinases, are preferentially expressed in basal-like and TNBC. Caveolins 1 and 2 have also been shown to predict response to platinum salts.

Basal-like tumors have been shown to be associated with neovascularization. Bevacizumab targets the vascular endothelial growth factor angiogenesis pathway. The Eastern Coopertive Oncology Group 2100 examined the addition of bevacizumab to taxanes in metastatic breast cancer patients, including those with TN phenotype. However, current results are not enough to comment on its effect on TN tumors. It has been reported that a subset of TN tumors, those with mesenchymal features, may benefit from TRAIL (tumor necrosis factor-resulting apoptosis-inducing ligand) inhibitors. Some of the ongoing trials are shown in the table.

Conclusion

TNBC and basal-like breast cancer are distinct molecular classes of breast cancer with a high degree of overlap. TN tumors can be identified in routine practice based on negative status for hormone receptors and HER2, while identification of basal-like cancer is still a challenge to pathologists. Given the fact that TNBC is such a heterogeneous entity, an important research field is the validation of immunohistochemical markers, enabling in better defining subgroups with different clinical behaviours and with predictive value towards sensitivity to chemotherapy and newer targeted treatments. The new challenge that arises is to use the immunohistochemical and genetic knowledge about these TNBCs to find tailored treatment regimens for this subgroup with limited treatment options and worse prognosis.

(Reviewed by Dr Suresh P, DNB student; Dr J B Sharma, Consultant; Dr D C Doval, Chief, Department of Medical Oncology & Director Research)

PERSPECTIVE

TRANSARTERIAL CHEMOEMBOLIZATION OF HEPATOCELLULAR CARCINOMA

Introduction

Transarterial chemoembolization (TACE) is a combination therapy of transarterial embolization and regional chemotherapy. Chemoembolization was proposed by KATO et al in 1981 in which intraarterial infusion of chemotherapeutic agents is combined with arterial embolization of the vascular supply of the neoplasm. Hepatocellular carcinoma (HCC) is a major health problem worldwide. It is the fifth most common cancer in the world, and the third most common cause of cancer-related deaths. Despite remarkable advances in the surveillance and treatment of HCC, a great proportion of patients are still not eligible for curative treatment due to an advanced tumor stage or poor hepatic functional reserve. For effective palliative treatments, TACE provides a survival benefit based on randomized controlled studies.

Principle

Liver is a unique organ with dual blood supply. It derives 70-80% of its supply from portal vein and remaining 20-30% from hepatic artery. Malignant tumors in the liver receive nearly all their nourishment from hepatic arterial supply, while normal hepatocytes are predominantly nourished by portal venous supply. These observations are the basis for the development of transarterial therapy for hepatic neoplasm while preserving normal hepatic functions. The combination of embolotherapy and regional chemotherapy has synergistic, anti-tumor effect with a high objective response rate. TACE reduces arterial inflow, diminishes washout of the chemotherapeutic agent, exposes the tumor to high concentrations of chemotherapy and confines the agents locally so that systemic toxicity is less. At the same time, this technique deprives the tumor of its blood supply, which can result in damage or death of the tumor cells.

Embolic Agents: Permanent embolic agents include polyvinyl alcohol (PVA) particles, microspheres and steel coils while gelatin sponges and autologous blood clots only embolize temporarily. Lipiodol is an iodinated ethyl ester of poppy seed oil having affinity for tumor neovascularity. It functions as microvessel embolic agent, carrier of chemotherapeutic agents and as augmenter of antitumor effect of TACE.

Chemotherapeutic Agents: These are usually suspended in iodized oil and are delivered as close to a tumor as possible followed by the embolization process. Several chemotherapeutic agents have been used, doxorubicin and cisplatin being the most common.

A novel system combining PVA bead and doxorubicin as drug-eluding beads (DEB), is supposed to release doxorubicin in a slow and controlled manner, improving pharmaco-kinetics of injected doxorubicin reducing drug-related side effects.

Indications

Chemoembolization is indicated in patients whose disease is predominately limited to the liver, whether the tumor began in the liver or spread to the liver from another organ. Hepatic neoplasms that are hypervascular in nature respond more favorably to chemoembolization than those lesions that are hypovascular. Cancers to be treated includes primary HCC, metastasis to the liver from colon cancer, breast cancer, carcinoid tumors, islet cell tumors of the pancreas, ocular melanoma etc. Chemo-embolization may be used as sole treatment, but has several limitations, with reduced efficacy for large tumors, so multimodal treatments are being developed in order to improve outcome. These include TACE Plus RFA, TACE and HCC Resection (before and after), TACE before liver transplant (LT), TACE to prevent drop out while awaiting LT, TACE for down staging HCC.

Patient Selection

TACE is usually done in a selected group of patients with multi-nodular HCC who cannot benefit from curative treatment. Pre-embolization assessment typically includes CT or MRI to evaluate the extent of intrahepatic disease and to exclude extrahepatic malignancy. Baseline laboratory studies should include a complete blood count, a prothrombin time, liver functions including bilirubin, creatinine, and any appropriate tumor markers. Preliminary diagnostic angiography of celiac and superior mesenteric artery is performed to assess the hepatic artery supply and to document the potency of the portal vein. In addition to the identification of variant hepatic arterial anatomy, identification of any parasitic arterial blood supply from adjacent organs and arterial supply to the gastrointestinal tract should also be done.

Procedure

An interventional radiologist usually carries out this procedure in close collaboration with an oncologist who

determines the amount of chemotherapy. Premedication with lorazepam 0.25 mg/kg orally 1 hour before the procedure is given. The procedure is done under local anesthesia with the help of image intensifier (a type of x-ray). 30-40 mg of 1% lidocaine is injected intra-arterially to reduce embolization-induced pain. A catheter is inserted into the femoral artery in the groin and is advanced via aorta into the hepatic artery. Once the branches of the hepatic artery that feed the liver cancer are identified, emulsion of 10 ml lipiodol, 5 ml omnipaque 300 (aids emulsifying the mixture), and a cytotoxic drug is used to embolize the tumor followed by particulate (PVC) embolization. Recently developed DC Bead mixed with equal volume of non-ionic contrast media shows good result. Maximum recommended dose is 75 mg/m^2 or a fixed dose of 150mg doxorubicin. The whole procedure takes one to two hours, and then the catheter is removed. Patient should be admitted and should be mobilized after 6 hours of bed rest. Postoperative antibiotics, anti-ulcer and analgesia are administered, if and when required by the patient. Some patients may undergo repeat sessions at 6 to 12 week intervals.

Benefits

TACE exposes tumor to high concentrations of chemotherapy and confines the agent locally, resulting in limited systemic toxicity. It stops tumour growth or shrinks them (lasting for average 10 to 14 months), and usually can be repeated if cancer starts to grow again. Other types of therapy (tumor ablation, chemotherapy, radiation, surgery) may be used in combination. Most importantly, it preserves liver function and maintains normal quality of life.

Contraindications

Hepatic embolization is contraindicated in the presence of hepatic encephalopathy or jaundice and compromised portal venous blood flow. Patients at higher risk of acute hepatic failure following arterial embolization include: extensive hepatic replacement by tumor, elevated lactate dehydrogenase, elevated AST and total serum bilirubin.

Risks & Complications

The most common complication of TACE is post-embolization syndrome that consists of transient abdominal pain and fever with elevated hepatic trans-aminases. It is self-limiting within 3-4 days. Hepatic failure after TACE is related to TACE-induced ischemic damage to the non-tumorous liver tissue.

Other less important complications are damage to the blood vessels, embolization material lodged in the wrong place, ischemic cholecystitis, hepatic abscesses and biliary strictures, upper gastrointestinal complications, allergic reaction to the contrast material, risk of kidney damage in patients with diabetes or other pre-existing kidney disease, reactions to chemotherapy (nausea, hair loss, cytopenia) etc.

Serious complications from TACE (either infection or damage to the liver) occur in about 1 in 20 procedures. Reports indicate that approximately one in 100 procedures result in death, usually due to liver failure.

Post-Procedural Imaging

Review CT is done 10-14 days following embolization and early if complications occur. Dense opacification (lipiodol) associated with necrosis is seen. It demonstrates non-target embolization and complications. Over time, reassessment should be done for collateral development which may contribute to tumor recurrence and may require repeat chemoembolization.

Survival Benefits

Llovet et al concluded that survival probabilities of HCC at 1 and 2 years were 82% and 63% for TACE and 63% and 27% for conservative treatment, respectively. Cumulative meta-analyses proved that TACE significantly reduced overall 2-year mortality rate compared to control patients on conservative/ inactive treatments. A recent study reported that 1-year and 2-year survival rates after TACE using DEB were 93% and 89%, respectively. Cheng et al recently showed that median survival with TACE-RFA was 37 months while that of TACE and RFA alone were 24 and 22 months, respectively.

Conclusion

TACE has been widely accepted as standard therapy in selected patients of HCC. Recent advancement in microcatheter technology has made it possible to perform ultra selective catheterization of tumor feeding arteries with reduced complication. With the advent of newer intra-arterial targeted agents, the potency of TACE has drastically increased. Further advances in the development of specific cancer therapeutics and drug delivery systems will provide a leap into the search for a cure against cancer.

(Reviewed by Dr Padma Talukdar, DNB student; Dr S Avinash Rao, Consultant; Dr AK Chaturvedi; Chief, Department of Radiology & Medical Director)

IN FOCUS

INDIA'S SUPERCONDUCTING CYCLOTRON

Introduction

Superconducting cyclotron is the most advanced and high tech accelerator. High speed charged particles circulating in the cyclotron are used by the scientists for frontline basic and applied research in nuclear sciences. Variable Energy Cyclotron Center (VECC) of the Department of Atomic Energy in Kolkata, India, has the expertise to construct a compact superconductor cyclotron for treatment of cancer. The foundation of supercyclotron project in VECC was laid in 1997. Only four laboratories in the world have a similar technology. With the cyclotron becoming operational in 2009, India is now in the world map possessing the most advanced technology and science in this aspect.

Principle

A large number of systems of the accelerator, mostly constructed in the country, are working in unison to give acceleration kicks to the tiny nuclei of oxygen. They get over 2500 acceleration kicks during their entire journey of about 7 km within the accelerator to attain full energy in about a few microseconds (microsecond=one millionth of a second).

Various Systems

The 100-tonne iron-core superconducting magnet produces magnetic field of about 5 Tesla. Over 8 tonnes of mass, consisting of the superconducting coil and stainless steel structures is continuously kept cool at-269^{0}C inside a most sophisticated 'Dewar' called the cryostat, kept in the iron-core. Over 35 km of superconducting wire has been used to construct the coil, winding its way round and round the bobbin. About 300 litres of liquid helium is required to keep the coil fully dipped at anytime. Thousands of litres of liquid nitrogen at -95^{0}C is also needed to keep the coils cooled at the operating temperatures.

The complex radiofrequency system gives acceleration kicks to the tiny particles. This system comprises of huge copper structures, called cavities, fabricated under strict quality control and a variety of high power electronic units. This system would deliver over 200 kW of radiofrequency power for acceleration of charged particles.

The tiny particles, covering several kilometres of distance during the process of acceleration, circulate in a chamber that is evacuated to a fraction of a millionth of a mm of mercury pressure. This pressure level is maintained with the help of a specially designed vacuum system. Ultra low pressure is also required to maintain high electric fields for acceleration of the particles. Hundreds of litres of very low conductivity water flows through various systems every minute to keep them cool. Performance of all the systems is monitored through the sophisticated computer control system from a set of control rooms. One important aspect of the superconducting cyclotron is its energy storage system, which stores energy in the form of magnetic fields in coiled superconducting wires. The stored energy can be released as and when required.

Applications of the Technology

The development has opened up application possibilities of the proton technology in various fields from cheap cancer treatments to energy storage. It is capable of delivering about 70 MeV (Million electron Volt) proton beam which is an ideal tool for treating melanoma of the eye and also brain tumors, which might not recur in five years. A superconducting cyclotron for cancer treatment using proton beams would be almost of the same size as the one constructed by VECC but with a simpler design. The superconducting cyclotron would offer highly challenging opportunities to young scientists and engineers who are getting ready with equally sophisticated experimental facilities for research. It also offers unique opportunities for material science research.

Future Perspective

The development of superconducting cyclotron has opened up application possibilities of the proton technology in various fields from cheap cancer treatment to energy storage. VECC is constructing first-of-its-kind medical cyclotron facility in the southern suburbs for production of thallium and gallium isotopes, which would come up within one year and it would be a big help to access fresh isotopes for those needing angioplasty, besides thyroid patients. Thus the superconducting cyclotron provides quantum jump in the accelerated particle energies for frontline experiments at par with their international counterparts.

(Reviewed by Dr P S Choudhury, Senior Consultant, Department of Nuclear Medicine)

RESEARCH & DEVELOPMENT

Breast Cancers Change Form

Scientists from the Breakthrough Breast Cancer Research Unit, University of Edinburgh, have discovered that over a third of breast cancer tumors change form when they spread. The researchers analyzed 211 tumors which had spread from the breast to the lymph nodes, in the armpit. They found that in 82 (39%) cases the disease in the lymph nodes had changed type. Twenty tumors changed from estrogen receptor (ER) negative to ER positive. This change would mean hormone therapies such as tamoxifen, which would not have worked for the orginal tumor, could help treat the disease if it has spread. Other tumors changed from ER positive to ER negative, which suggests those patients may be given treatments which will not benefit them, and are therefore experiencing side effects unnecessarily. They were surprised that such a high proportion of tumors change form when they spread beyond the breast. This suggests that there is a need to test which type of disease a woman has in the lymph nodes, because it could radically alter the course of treatment she receives. Clinical trials need to be carried out to see how these results could benefit patients.

(Annals of Oncology, Nov 4, 2009)

Cancer Risk in Type 2 Diabetes Mellitus

A research team at the Veterans Affairs Medical Center, California, conducted a comprehensive assessment of the risk for gallbladder, biliary and pancreatic cancers in a large cohort of patients with type 2 diabetes mellitus (DM).The team performed a retrospective search of type 2 DM patients matched to non-diabetic controls from 1990 to 2000, for the presence of gallabladder, billary and pancreatic cancer. The database search identified 1,172,496 cases and control subjects for analysis. Among patients with type 2 DM, the incidence of pancreatic cancer was increased three-fold compared to controls and gallbladder and extrahepatic biliary cancers were increased by two-fold compared to controls. This study suggests future avenues for investigation to determine preventive measures and screening implementation strategies to limit the impact of these tumors in the veteran as well as general type 2 DM population in the United States.

(World Journal of Gastroenterology, Nov 14, 2009)

Circulating Tumor Cells

Researchers at the University of California-Los Angles (UCLA), have developed an innovative new device with nano-sized features to capture circulating tumor cells (CTCs). It can provide critical information for examining and diagnosing cancer metastasis, determining patient prognosis, and monitoring the effectiveness of therapies. The device grabs cancer cells in the blood that have broken off from a tumor, just as fly paper captures insects. To date, several methods have been developed to track these cells, but the UCLA team's novel "fly paper" approach may be faster and cheaper than others; it appears to capture far more CTCs. The UCLA team developed a 1-by-2-centimetre silicon chip that is covered with densely packed nanopillars. The nanopillar chip captured more than 10 times the amount of cells captured by the currently used flat structure. The study found an optimal detection time of only 2 hours using nanopillar chips. Further studies with "break-away" cancer cells in patients' blood, as well as in other body fluids, such as urine and abdominal fluids, are required.

(Medical News Today, Nov 20, 2009)

Sprycel for Ovarian Cancer

Researchers at the Jonson Comprehensive Cancer Center have found that the drug Sprycel, approved for use by the US Food & Drug Administration in patients with chronic myeloid leukemia, significantly inhibited growth and invasiveness of ovarian cancer cells and also promoting their death. Sprycel, also known as a "dirty" kinase inhibitor, inhibits more than one pathway. It inhibits the focal adhesion kinase and ephrin receptor, also associated with ovarian cancer. In this study, the drug was tested against 34 ovarian cancer cell lines, on which genetic analysis was conducted. The researchers were thus able to identify genes that predict response to Sprycel. If the work is confirmed in human studies, it may be possible to test patients for Src activation and select those who would respond prior to treatment,thereby personalizing their care. The drug, when paired with a chemotherapy regimen, was even more effective in fighting ovarian cancer in cell lines in which signaling of the Src kinases, associated with the deadly disease, is activated. It may be possible to add the targeted therapy as a first line treatment if its efficacy is confirmed in future studies, adding a new tool to an oncologist's arsenal.

(BMJ, Nov 10, 2009)

NEW TECHNOLOGIES

DRUGS

New Drug Regimen

For patients with advanced biliary-tract cancers, systemic chemotherapy is the standard treatment. A study reports that bevacizumab given in addition to the combined chemotherapy regimen of gemcitabine and oxaliplatin (GEMOX-B) is well tolerated. It also shows promising antitumor activity in patients with advanced biliary-tract cancers as compared to patients treated with GEMOX-B alone. A Phase 2 trial investigated the effectiveness and safety of GEMOX-B in patients with biliary-tract cancers. Researchers also examined the potential of changes in whole body PET scans as an early predictive marker of clinical outcome, to help identify patients most likely to benefit from the treatment. A total of 35 patients with advanced biliary-tract cancers were given all 3 drugs intravenously. At start of trial and at the end of second cycle of therapy, whole body PET scans were done and results indicated good tumor response. These findings support the combination of molecularly targeted agents with chemotherapy to further improve treatment outcomes in patients with biliary-tract cancers.

(Medical News Today, Nov 23, 2009)

New Leukemia Drug

Chronic lymphocytic leukemia (CLL) accounts for about one-third of all leukemias. Ofatumumab, manufactured by GlaxoSmithKline and Genmab, is a monoclonal antibody that helps stimulate the immune system to fight cancer cells. It works by binding to a specific protein found on both normal and malignant B cells. The drug ofatumumab (Arzerra) was given fast-track approval by the US FDA for the treatment of CLL that is not responding to fludarabine (Fludara) or alamtuzumab (Campath). The FDA's approval of ofatumumab was based on encouraging results from a single-arm study of 59 patients whose CLL had come back or was not responding to other treatments. Forty-two percent of the patients responded to ofatumumab. The average response time was 6.5 months, the most serious side effect being an increased chance of infections. GlaxoSmithKline plans further studies of the drug.

(American Cancer Society News, Oct 29, 2009)

Omacetaxine Mepesuccinate

Chronic myeloid leukemia (CML) patients initially respond well to treatments with drugs called tyrosine kinase inhibitors (TKIs). However, a significant proportion of patients fail, or become intolerant to, one or more TKIs, and the cause of failure may be traced to the emergence of Bcr-Abl mutations. A common mutation called T315I renders CML resistant to all currently approved TKIs. This has created a significant unmet medical need in the management of CML. Omacetaxine mepesuccinate is used for the treatment of CML patients who have failed treatment with imatinib and who have developed the Bcr-Abl T315I mutation. ChemGenex's filing of marketing authoriztion application, based on data from pivotal study 202 where omacetaxine mepesuccinate demonstrated clinical benefit for the treatment of T315I positive CML patients, was validated by the European Medicines Agency. Omacetaxine specifically binds to ribosomal A-site cleft, inhibiting protein translation of short-lived oncoprotiens that are upregulated in leukemic cells (particularly Cyclin-D1, Mcl-1 and c-Myc) and also kills human CML stem cells known to be insensitive to TKIs. Omacetaxine is currently in global Phase 2/3 clinical trials for CML and has been granted Orphan Drug designation by US FDA and European Medicines Agency (EMEA) as well as Fast Track status by the FDA.

(ChemGenex Pharmaceuticals Ltd, Nov 30, 2009)

Oncophage® Cancer Vaccine

Many patients with glioblastoma survive less than one year after diagnosis. As a result, researchers continue to evaluate new and innovative treatment strategies. Oncophage® is an investigational anticancer vaccine that is derived from the patient's own tumor. The vaccine is intended to prompt the body's immune system to respond to the cancer cells without affecting healthy cells. The safety and efficacy of Oncophage® for the treatment of recurrent or progressive high-grade glioblastoma is being evaluated in a Phase 2 clinical trial. Preliminary results from the clinical trial show that among patients with recurrent or progressive high-grade glioblastoma, treatment with the investigational Oncophage® (vitespen) cancer vaccine may improve survival. In the first 20 patients treated with Oncophage®, median survival was 10.1 months. Thirty percent of patients survived for one year or longer. It suggests that Oncophage® may be a promising treatment approach for patients with recurrent or progressive glioblastoma.

(Cancer Consultants News, Nov 4, 2009)

TECHNIQUES

Interventional Neuro-Oncology

Neurosurgeons from NewYork-Presbyterian Hospital/Weill Cornell Medical Center performed the world's first intra-arterial cerebral infusion of Avastin (bevacizumab) directly into a patient's malignant brain tumor. This novel technique may expose the cancer to higher doses of the drug therapy, while possibly sparing the patient's common side effects of receiving the drug intravenously or throughout their body. To deliver the drug, neurosurgeons direct a hair-thin microcatheter through blood vessels in the body, via the carotid artery running up the neck, and then into the smaller arteries deep in the brain. Upon arriving at the tumor site, a drug to open the blood-brain barrier is injected. After the blood-brain barrier is temporarily opened, a window of time lasting approximately 5minutes, the chemotherapeutic agent Avastin is injected directly into malignant tumor. The investigative procedure, called super selective intra-arterial cerebral infusion of Avastin, has been successfully performed on 5 patients with promising results. Researchers are currently enrolling patients for the Phase 1 study. This technique may herald birth of a new field of "Interventional Neuro-Oncology."

(Medical News Today, Nov 18,2009)

New Way to Brain Tumor Biopsy

Neurosurgeons at Barrow Neurological Institute at St. Joseph's Hospital and Medical Center are using the new miniature laser confocal microscope to view brain tumor regions during surgery and obtain digital images of the tumor and brain tissue. The microscope is used to image the tissue after a fluorescent drug injected into the patient travels into the tumor. It was possible to distinguish cancer cells and the margin of the brain tumor without taking a biopsy and to obtain a digital video of the brain tumor to show blood flowing through the abnormal vessels of the tumor and the transition from normal to abnormal brain tissue. Intraoperative diagnosis is performed by obtaining several specimens from within a brain tumor using biopsy forceps and cutting, freezing and staining the specimen for examination under the microscope. The traditional analysis is limited by sampling error and by mechanical tissue damage from the biopsy forceps, slowing operative workflow by 30 to 40 minutes. The new microscope can overcome these limitations by helping to visualize the cellular and tissue features of a tumor in real-time. The probe can be moved over the entire visible extent of a tumor, guiding the neurosurgeon to hypercellular or aggressive areas that are likely to generate high-yield biopsies.

(St. Joseph's Hosp. and Med. Center , Nov 11, 2009)

Optical Biopsy for Breast Cancer

A University of Florida biomedical engineering researcher is making progress on an "optical biopsy" for breast cancer that has the potential to determine whether growths are cancerous without ever puncturing the skin. It is highly likely it can become a diagnostic tool, an adjunct to x-ray mammography. Phase-contrast diffuse optical tomography is a screening technology that roots out breast cancer with light and computing power. Light from the harmless lasers enters the breast and scatters. There is sufficient data for computer algorithms to create an image of the breast's interior. This image suggests either benign conditions or some of the telltale signs of cancer that are completely invisible to standard x-ray mammograms, for example, a high density of blood vessels snaking around a likely tumor. Light collected from collisions can indicate chemical evidence of cancer and index refraction or phase contrast technique provides information on cellular size and density. The technique correctly identified biopsy confirmed malignancies nearly 75% of the time with the most accurate results from older patients, whose softer breasts make abnormalities more prominent. The research has since boosted the accuracy rate to 91% in a study involving 144 women.

(University of Florida, Nov 6, 2009)

Transaxillary Thyroid Surgery

New form of endoscopic surgery performed in Tulane University School of Medicine uses a small incision under the arm to remove all or a portion of the thyroid or parathyroid glands without leaving a scar on the neck. This exciting new treatment option, approved by the US Food and Drug Administration in 2009, uses the latest Da Vinci® three-dimensional, high definition robotic equipment to make a two-inch incision below the armpit that allows doctors to maneuver a small camera and specially designed instruments between muscles to access the thyroid. The diseased tissue is removed endoscopically through the armpit incision. This technique safely removes the thyroid without leaving so much as a scratch on the neck. Traditional thyroidectomies can involve a long incision at the base of the neck.

(Science Daily, Nov 25, 2009)

CLINICAL TRIALS

Eribulin Mesylate

Eisai Inc. announced preliminary results from a recently completed global Phase 3 study with eribulin mesylate in patients with locally advanced or metastatic breast cancer. Eribulin is a new chemical compound and is a synthetic analogue of halichondrin B, a naturally-derived compound that was first isolated from a marine sponge. The study known as "EMBRACE"(Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) was an open-label, randomized, parallel two-arm multi-center study of 762 women with locally recurrent or metastatic breast cancer previously treated with at least 2 and a maximum of 5 prior chemotherapy regimens, including an anthracycline and a taxane. The patients were treated either with eribulin or with treatment of physician's choice. Preliminary results from the study demonstrated a statistically significant improvement in overall survival in eribulin-treated patients compared with the physician's choice of therapy. The most common adverse event reported was myelosuppression.

(Eisai Inc., Oct 31, 2009)

Herceptin® for Stomach Cancer

According to the results of a Phase 3 clinical trial, Herceptin® (trastuzumab) improves survival among patients with HER2-positive, advanced and inoperable stomach cancer. Herceptin targets and blocks the HER2-protein, and is used for the treatment of both early-stage and more advanced HER2-positive breast cancer. HER2 is also overexpressed in some stomach cancers. Researchers conducted an international Phase 3 clinical trial study among 594 patients with HER2-positive, advanced and inoperable stomach cancer. Half the patients were treated with chemotherapy alone, and the other half were treated with chemotherapy plus Herceptin. Chemotherapy consisted of a fluoropyrimidine (Xeloda® [capecitabine] or 5-FU) and cisplatin. Overall survival was 13.8 months among patients treated with chemotherapy plus Herceptin compared with 11.1 months among patients treated with chemotherapy alone. Patients whose tumors had the highest levels of HER2 appeared to derive the most benefit from Herceptin.

(UFSCC News, Sep 25, 2009)

Lymphoseek Phase 3 Trial

The Phase 3 Lymphoseek clinical trial (NEO3-05) results confirm the identification of lymphatic tissue in breast cancer patients with either breast cancer or melanoma as designed, and when used in conjunction with and compared to vital blue dyes, showed a marked improvement in this identification. Pathological assessment of lymphatic tissue removed during surgery provided further prognostic value in determining the disease state. The trial was designed to determine the accuracy of Lymphoseek to identify lymphatic tissue as compared to commonly used vital blue dyes. The primary objective of the trial was to obtain at least 203 lymph nodes identified with the vital blue dyes and to statistically demonstrate that 94% of those nodes were identified with Lymphoseek. Procedure-compliant patients in the trial contributed 215 vital blue positive nodes and Lymphoseek identified 210 of those nodes for a success rate of over 97%. Lymphoseek also identified 85 lymph nodes that were missed by the vital blue dyes. Of these Lymphoseek positive nodes, over 18% were found by pathology to contain tumor. The filing of end-of-Phase 3 report is a milestone in the development process for Lymphoseek.

(Neoprobe, Dec 9, 2009)

Prostate Cancer

Investigators presented, at the 10th Annual Meeting of the Society of Urolozic Oncology, the results for prostate-specific (PSA) antigen recurrence from the additional analysis of secondary end points of biochemical recurrence rate in a Phase 3 pivotal study of FIRMAGON® (monthly degarelix for injection) or monthly leuprolide in prostate cancer patients during the first year of treatment. Prostate cancer patients who received FIRMAGON® 240/80 mg/month had a recurrence rate of 7.7% during the first year of treatment compared with 12.9% of patients treated with leuprolide 7.5 mg/month (p=0.05). Patients being treated with FIRMAGON® also had longer time to recurrence compared with those on leuprolide (p=0.04). Results of the multicenter, randomized, open-label trial, comparing degarelix with leuprolide in prostate cancer patients, showed that degarelix is as effective as leuprolide in reducing and sustaining castrate levels of testosterone. Suppression of testosterone to castrate levels occurred significantly faster in patients receiving degarelix than in those receiving leuprolide. Study also showed that degarelix achieved faster suppression of luteinizing hormone and follicle-stimulating hormone.

(Drugs.com, Dec 4, 2009)

WATCH-OUT

Anti-cancer Agent

Pateamine A (PatA), a natural product first isolated from marine sponges, has attracted attention as a potential anti-cancer agent. It has been found to inhibit surveillance mechanism called NMD (Nonsense-mediated mRNA decay), a key mechanism in the cell to degrade damaged and not fully functional mRNA. NMD watches inside the body 24 hours a day, and whenever damaged mRNA is found, NMD attaches a "bad-mRNA" tag on it and summons an army to destroy it. Researchers found that PatA and a simplified, easier to synthesize derivative of PatA called desmethyl, desamino-PatA (DMDAPatA) inhibits NMD. This may contribute to the apoptosis of tumor cells. Group in 2005 using a PatA conjugate, found that PatA inhibits the initiation phase of protein synthesis which gives PatA the potential to fight cancer. Tumor cells are more vulnerable to DMDAPat's inhibition of protein synthesis, making it a good candidate as an anti-cancer agent. It has been patented by Texas A&M, evaluated as a potential anti-cancer agent for both human and animal (pet) applications.

(Texas A & M University, Nov 2,2009)

Biomarkers for Ovarian Cancer

Vermillion, Inc., California, announced on November12, 2009 that the US Patent Office has issued a patent, number 7, 605, 003, titled "Use of Biomarkers for Detecting Ovarian Cancer" to the company for the discovery of biomarkers for ovarian cancer. Patent covers biomarker combinations for both diagnosis and management of ovarian cancer and covers measurement of markers by a variety of methods, including mass spectrometry and immunoassay approaches. The OVA1 Test is a qualitative serum test that combines the results of five immunoassays into a single numerical score. It is indicated for women who meet the following criteria: over age 18, ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. It utilizes 5 well-established biomarkers-Transthyretin, Apolipoprotein A-1, Beta2-Microglobulin, Transferrin and Cancer Antigen 125 and a proprietary algorithm to determine the likelihood of malignancy in women with pelvic mass for whom surgery is planned.

(Biocompare News, Nov 12, 2009)

Marker for Colorectal Cancer

European Patent Office has assigned Patent Publication No. US2009286328 (A1) to Wild Norbret (DE) et.al, entitled"Use of Protein S100A12 as a Marker for Colorectal Cancer", published on Nov 19, 2009. Early detection procedures for colorectal cancer available at present involve using tests for fecal blood or endoscopic procedures. It was the task of the present invention to investigate whether a new marker can be identified which may aid in CRC diagnosis. Preferably such marker would be present in stool and allow for a non-invasive diagnosis. Surprisingly, it has been found that the use of the protein S100A12 as a marker for CRC can at least partially overcome the problems. The present invention, therefore, relates to a method for the diagnosis of colorectal cancer comprising the steps of (a) providing a stool sample obtained from an individual; (b) contacting said sample with a specific binding agent for S100A12 under conditions appropriate for formation of a complex between said binding agent and S100A12 ;(c) determining the amount of complex formed in step (b); and (d) correlating the amount of complex determined in (c) to the diagnosis of colorectal cancer.

(European Patent Office, Dec 3, 2009)

Monitoring Treatment Response

Norfray Joseph F. (Glenview,IL) the inventor, has been assigned US Patent No. 7622102 entitled "Method for monitoring early treatment response", published on November 24, 2009. The invention provides a method for monitoring early treatment response of a cancer treatment comprising measuring by magnetic resonance spectroscopy (MRS), for example, proton MRS, the amount of choline present in the tissue adjoining or surrounding the cancerous tissue before and after treatment; the treatment comprises administration of an angiogenesis inhibitor, whereby a decrease in the amount of choline after treatment is indicative of a positive response. The invention also provides a method for determining effectiveness of an angiogenesis inhibitor in the treatment of cancer. Also disclosed are methods of monitoring early treatment response in diseases where an angiogenesis effector is employed. The present invention offers the combined advantages of MRI and MRS and also provides a method for monitoring cancer treatment, especially a treatment of cancer susceptible to metastasize.

(USPTO, Nov 30, 2009)

GLOBE SCAN

Plan to Regrow Breasts

Australian scientists have developed a surgical technique, known as Neopec, that may allow cancer-suffering women to regrow their breasts after having a mastectomy. Human trials are planned to start within three to six months. The procedure involves inserting a breast-shaped chamber, containing a sample of the woman's fat tissue, under the chest skin. A blood vessel is then connected to the fat tissue, allowing it to grow to fill the chamber within six to eight months. The procedure relies on the body's own behavior of filling internal voids, but a gel-like substance can also be injected to stimulate fat growth. Five women are set to undergo the experimental surgery at St Vincent's Hospital in this prototype trial. The women in the trial have had a mastectomy or partial mastectomy, but there remains a defect or asymmetry issue with their breasts. The trial will not seek to grow a whole breast, but grow fat in the defected area to prove the procedure is viable and it can also be used to help restore other damaged body parts. The new procedure, if successful, would be an important step forward in dealing with breast cancer.

(Australia: Reuters, Nov 11, 2009)

Cancer Causing Substances

Recently a group of thirty leading scientists met at the International Agency for Research on Cancer (IARC) to discuss a number of substances that can cause cancer. They found more cancers linked to tobacco and alcohol. Bowel and ovarian cancers have now been added to the list of cancers caused by tobacco smoking, while recent studies also suggest a small positive association of smoking with breast cancer. Research has confirmed that parents's smoking can cause childhood cancer, and children born to smokers face a higher risk of a rare form of cancer called hepatoblastoma. There also appears to be an increased risk of leukemia in children whose fathers smoked before their conception. IARC confirms that secondhand smoke can cause lung cancer and notes that there is some evidence for a link between cancers of the larynx and pharynx. Smokeless tobacco has now been shown to cause cancers of the esophagus, mouth and pancreas. IARC experts also looked at the cancer-causing potential of betel quid which can cause esophageal cancer, and limited evidence for an association with liver cancer. The report finds some evidence that alcohol may cause pancreatic cancer. The existing list of cancers linked to drinking includes cancers of the mouth, pharynx, larynx, esophagus, bowel, liver and breast. There is also now enough evidence to say that acetaldehyde, a chemical that is produced when alcohol is broken down in the body, can cause cancer. This strengthens the evidence on how alcohol and cancer are linked.

(France: Cancer Research UK, Nov 4, 2009)

New Mammography Recommendations

The US Preventive Services Tasks Force (USPSTF) has reversed its position on screening mammography for women in their 40s. The group no longer recommends routine screening mammography for average-risk women in this age group. The most important potential benefit of screening mammography is a modest reduction in breast cancer mortality. Potential risks of mammography include false-positive test results (which lead to stress and additional testing), false-negative test results (a missed cancer), and overdiagnosis. Young women are more likely than older women to experience some of the downsides of mammographic screening, and are also less likely to have breast cancer. The fact that the USPSTF and the American Cancer Society now have different screening recommendations for women in their 40s, simply reinforces the importance of educating oneself about the potential risks and benefits of screening, talking with the physician, and making the right decision. This point is highlighted by the USPSTF, which notes, "The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms."

Other highlights of the new USPSTF recommendations include: (i) For women between the ages of 50 and 74 years, mammography to be done every two years (rather than every year).(ii) There is insufficient evidence to assess the benefit and harms of screening in women over the age of 74. (iii) The USPSTF recommends against teaching breast self-exam.

Recent discussion regarding mammography recommendations is focused on women at average risk of breast cancer. Women at increased risk as a result of family or personal history may need to begin screening at a younger age.

(US: USPSTF, Nov 17, 2009)

ACTIVITIES OF RGCI&RC

Cervical Cancer Awareness

Introduction

Cervical cancer is a major global public health problem affecting socio-economically deprived population. It is the most common cancer among women in low-resource countries (85% of global cervical cancer burden of approximately 4,93,000 cases and 2,73,000 deaths annually). In India, it is estimated that approximately 100,000 women develop cervical cancer each year. Cancer cervix occupies either the top/second rank among cancers in women in developing countries. One out of every twenty women dying of cancer cervix is an Indian.

In many developed countries, a decline in the incidence and mortality due to cervix cancer has been observed in the past 30 years due to implementation of a number of cancer screening programs. In India, it is difficult to arrange such programs because of reasons like absence of trained manpower, infrastructure, logistics, quality assurance, frequency of screening and costs involved. National health managers are trying to organize cytological screening programs through regional cancer centres. Human papilloma virus (HPV) vaccines have been launched recently to prevent infection by the two major types of HPV causing cervical cancer.

Facts about Cervical Cancer

- Cervical cancer forms in tissues of the cervix and a continuum of pathological changes may be diagnosed, ranging from atypical squamous cells of undetermined significance (ASCUS) to low grade squamous intraepithelial lesion (LSIL) to high grade squamous intraepithelial lesions (HSIL) to invasive cancer. The precancerous conditions LSIL and HSIL are also referred to as cervical intraepithelial neoplasia (CIN)1,2 and 3. Lesions can regress, persist or progress to an invasive malignancy, with LSIL (CIN 1) more likely to regress spontaneously and HSIL (CIN 2/CIN 3) more likely to persist or progress. The average time of progression of CIN 3 to invasive cancer is estimated to be 10 to 15 years.
- Early symptoms include irregular bleeding from the vagina, increased vaginal discharge, brown or blood stained vaginal discharge.
- Cervical cancer occurs in women with early age marriage (<18 years). Disease increases from 35 years and reaches a peak between the age of 55 to 64 years. CIN, the precursor lesion to cervical cancer, occurs in much younger women.
- Most of the cancers present in advanced stages rather in early stages. Clinical stage at presentation is the single most important variable in predicting survival.
- Regular Papanicolau (Pap) tests are essential for detecting abnormalities before they become cancerous. Most invasive cervical cancers are found in women who have never been screened or have not had a Pap test within the past 5 years.

Risk Factors

The most important risk factor for cervical cancer is infection by certain types of HPV. These include HPV types 16, 18, 31, 33 and 45 along with several others. HPV 16 and 18 account for about two-thirds of all cervical cancers. Some patterns of sexual behavior increase a women's risk of getting HPV; namely, sex at an early age, having many sexual partners, having a partner who has had many sexual partners and having sex with uncircumcised males. The vast majority of women who have been infected would never get the disease. In addition to HPV infection, the risk factors for cervical cancer include poor genital hygiene; cigarette smoking; weakened immune system; oral contraceptives and multiple full-term pregnancies. Some studies have shown that Chlamydia infection and diets low in fruits and vegetables may also increase risk.

Risk Reduction

Women have a choice between US Food &Drug Administration (FDA) approved vaccines-gardasil and cervarix. Gardasil is Merck's quadrivalent vaccine (HPV 6/11/16/18) and cervarix is Glaxosmithkline's bivalent vaccine (HPV 16/18). However, vaccination is not a substitute for screening with Pap tests. Even in women who have been vaccinated, non-HPV type of cervical cancer may develop.

The American Cancer Society Recommendations

According to the American Cancer Society ACCP, cervical cancer screening should begin approximately 3 years after a woman begins having vaginal intercourse, but no later than the age of 21 years. Screening should be performed every year with conventional Pap tests or every 2 years using liquid-based Pap tests. At or after 30 years age, women who have had 3 normal test results in a row may get screened every 2 to 3 years with cervical

cytology alone or every 3 years with a human papilloma virus DNA test plus cervical cytology. Women aged 70+ years who have had 3 or more normal Pap tests and no abnormal Pap tests within the last 10 years and women who have undergone a total hystrectomy may choose to stop cervical cancer screening.

Cervical Cancer Tests

Cytology Tests: Cytology tests include conventional Pap smear and liquid based cytology (LBC) method. Conventional Pap smear has been regarded standard for cervical cancer screening programseven though sensitivity is only 52%. LBC is associated with a reduction in the incidence of inadequate cervical smears. LBC is done as the thin Prep slide by an automated computerized system. In conventional Pap test, cells from a woman's cervix are smeared on a microscope slide. In the LBC method, cells are placed in a vial containing a special preservative to provide a well preserved sample that is automatically transferred to a slide. Both types of tests can detect pre cancers before they can turn into invasive cancers. Cytology tests are good but not perfect. If these tests detect abnormal cells, further procedures are necessary to confirm the diagnosis. These procedures include colposcopy and dilatation and curettage.

Visual Screening*:* Visual inspection of the cervix after application of 4-5% acetic acid (VIA) is a simple, inexpensive test that can be provided by trained health workers. The accuracy of VIA to detect cervical neoplasia hasbeen extensively studied and found to be satisfactory. It is an extremely useful test which can be performed by health workers after a very short training. Positive patients can be referred to a doctor for further management.

Molecular Diagnostic Approach: Between 93-100% of squamous cell carcinomas of the cervix contain DNA from high risk types of HPV which are transmitted during sexual activity. Research has shown that tests for HPV may be a useful addition to Pap tests in women older than 30. The Hybrid Capture II HPV test is approved by the FDA to determine the presence of the types of HPV that cause cervical cancer. The benefit of the HPV test is that when used in conjunction with the Pap smear, it can categorically confirm whether patients with abnormal results are at risk of developing cervical cancer.

Treatment

It varies with the stage of the disease. For early invasive cancer, surgery is the treatment of choice. In more advanced cases, radiation combined with chemotherapy is the current standard of care. In patients with disseminated disease, chemotherapy or radiation provides symptom palliation.

HPV Vaccine

This vaccine is now available for prevention of HPV-associated dysplasias and neoplasia, including cervical cancer, genital warts (condyloma acuminata), and precancerous genital lesions. The immunization should be administered to girls and young women aged 9-26 years and even till 45 years of age.

Prognosis

Prognosis of cervical cancer depends on disease stage. In general, the 5-year survival rate for stage I disease is higher than 90%; for stage II, it is 60-80%; for stage III, it is approximately 50%; and for stage IV disease, it is less then 30%.

Patient Education

Screening younger women is an important strategy for preventing cervical cancer and adequately treating precancerous lesions. Most of the deaths can be prevented if more women get tests to detect cervical cancer early. It is imperative to increase awareness about the benefits of Pap test screening.

Cervical Cancer Awareness Month in RGCI&RC

Cervical cancer awareness month was observed in the month of November 2009 and free Pap tests were done in Preventive Oncology OPD as part of screening program. A movie were shown on cancer awareness to patients and their attendants. Altogether, 140 females got Pap test done in OPD & Gender Resource Centers, out of which 5 females had ASCUS and LSIL Pap test. Colposcopy and biopsy were also done.

Reiterating its commitment towards spreading awareness about cancer, Rajiv Gandhi Cancer Institute & Research Centre was present at the India International Trade Fair 2009 and had set up a stall at the Health Pavilion under the Ministry of Health & Family Welfare (MoH&FW). More than 700 people visited the stall and were made aware about cancer, its symptoms, prevention and regular screening programs. Senior officials from MoH&FW also visited the stall.

(Reviewed by Dr Sudhir Rawal, Senior Consultant, Dr Rupinder Sekhon, Consultant, Department of Genito-Uro Oncology, Dr Rajni Mutneja, Head, Department of Preventive Oncology)

MicroRNAs In Cancer Diagnostics

Dr Mahesh Mansukhani, Associate Professor of Clinical Pathology, Columbia University Medical Center, Columbia University, New York, USA, visited Rajiv Gandhi Cancer Institute & Research Centre on Nov 9, 2009 and delivered a lecture on 'microRNA-Upcoming Significance in Cancer Diagnostics'. The lecture was attended by the Medical Director, Consultants, DNB students and Research Officers of the Institute.

microRNAs (miRNA) are endogenous~22 nucleotide RNAs and a recently-discovered family of human genes. These are short sequences of RNA (ribonucleic acids) that are not translated into proteins, rather they are incorporated into protein complexes, and act to silence other (protein-coding) genes. The levels of miRNAs in cells have been shown to be very specific to different types of tissues and tumors. miRNAs are excellent biomarkers for molecular cancer diagnostics because their number is high in food chain. Today, more than 500 human miRNAs have been experimentally identified. They are highly tissue specific and are stable markers in formalin fixed paraffin embedded (FFPE) tissues. Using proprietary methods developed by Rosetta Genomics, miRNAs can be extracted from a wide range of tissues and quantified to identify a specific miRNAs signature.

Dr Mansukhani explained that in this era of targeted therapies, it is very important to get the accurate diagnosis of the disease. He explained about the cutting edge molecular tests; miRview™ squamous test, miRview™ mets and the miRview™ meso test.

miRview™ squamous - uses miRNA to accurately differentiate squamous from non-squamous non-small cell lung cancer (NSCLC), helping to make informed decisions. Out of NSCLC, 30% are squamous and 70% are non-squamous cells. Current methods of differentiating squamous from non-squamous NSCLC are not standardized, are difficult to reproduce and have low accuracy. Studies that reviewed the accuracy and reproducibility of histopathological classification of lung cancer, found that 30%-40% of samples were misclassified. miR-205 and miR-21 are markers of squamous cell carcinoma. miRview squamous provides a differential diagnosis with fast, standard and objective classification; the highest level of accuracy (91% specificity and 97% sensitivity); simple interpretation and routine sample preparation.

miRview™ mets - It identifies the tissue-of-origin of metastatic tumors. Oncologists and pathologists are often faced with a diagnostic dilemma when trying to identify metastasis from unknown origin or primary site. Current diagnostic methods include a wide range of costly, time consuming and at times inefficient tests, including histopathology analysis of the biopsy and imaging methods, such as chest x-ray, CT and PET scans for'Cancer of Unknown Primary' (CUP). miRview™ mets applies the benefits of miRNA biomarkers for the identification of tumor origin. The test identifies 25 different tumor types, including but not limited to tumors with the following tissue origins: colon, liver, brain, breast, kidney, lung, ovary, pancreas, prostate and testis. The test leverages proprietary miRNA technology developed by Rosetta Genomics and measures the expression level of 48 microRNA biomarkers.

The technology includes protocols for the extraction of miRNA from FFPE tissue samples and quantification of the relative amounts of various miRNA biomarkers using quantitative real-time polymerase chain reaction technology. The miRview™ mets uses a combination of a decision-tree with a K-nearest-neighbour classifier. The test generates either a single, high-confidence prediction or two lower-confidence predictions for the tissue-of-origin of the tested samples. In the majority of cases, miRview™ mets returns a single tissue prediction with 90% sensitivity and 99% specificity.

miRview™ meso - is a test designed to differentiate malignant pleural mesothelioma from peripheral adenocarcinoma of the lung or metastatic carcinomas involving the lung pleura. Accurately diagnosing mesothelioma currently presents a challenge to the physicians and there is no single diagnostic test that is entirely conclusive for either malignant mesotherlioma or metastatic tumor. The pathological diagnosis may suffer from the absence of specific and reliable markers and mesothelioma can be difficult to identify from other cancers. miRview™ meso leverages proprietary miRNA technology and measures the expression level of three microRNA biomarkers to differentiate patients that have mesothelioma of the lung-pleura from patients that have non-mesothelioma tumors in the lung-pleura. It provides accuracy (the sensitivity and specificity of miRview™ meso have been shown to be 95% and 96% respectively).

Dr Mansukhani's presentation was well appreciated and the Medical Director thanked him for the very informative lecture.

Workshop on Uro-Oncology

A two-day workshop on 'Uro-Oncology' was conducted by the Genito-Uro Oncology Unit of the Department of Surgical Oncology, Rajiv Gandhi Cancer Institute and Research Centre (RGCI&RC) on 12th and 13th December 2009, under the guidance of Dr Sudhir Rawal, Senior Consultant, Genito-Uro Oncology. It was attended by eminent urologists from Delhi and North India. The workshop was inaugurated by Dr K.V. Swaminathan, Chairman, RGCI&RC and Mr D.S. Negi, CEO, RGCI & RC, welcomed the delegates.

The workshop commenced with a lecture by Dr Rawal on 'Treatment Options for Organ Confined Carcinoma Prostate' and 'Role of High Intensity Focused Ultrasound in Carcinoma Prostate'. This was followed by live demonstration, by Dr Rawal, of 'Radical Cystoprostatectomy with Pitcher Pot ileal Neobladder' in a case of muscle invasive carcinoma urinary bladder, which was well received by the audience. Post lunch, there was lecture by Dr Rajeev Sood, Professor Dr Ram Manohar Lohia Hospital & PGIMER, on 'Treatment for Hormone Refractory Prostate Cancer'. The first day of the workshop ended with an enlightening talk on 'Role of Radiotherapy in Localised and Locally Advanced Prostate Cancer' by Dr Vivek Bansal, Senior Consultant, Department of Radiotherapy, RGCI&RC.

The second day of the workshop began with a lecture on 'Management of Renal Cell Carcinoma with Thrombus in Renal Vein and Inferior Vena Cava' by Dr Amlesh Seth, Professor, AIIMS. It was followed by another lecture on 'Management of Metastatic Renal Cell Carcinoma' by Dr N.K. Mohanty, Professor, Safdarjung Hospital and Vardhman Mahavir Medical College, a live demonstration of surgery 'Retroperitoneal Lymphnode Dissection' in a case of non-seminomatous germ cell tumor with post chemotherapy Retroperitoneal Lymph Node Residue, by Dr Bijoy Abraham, Professor Dr B.L. Kapoor Hospital. The session concluded by a video presentation on 'Radical Retropubic Prostatectomy'.

The workshop was well appreciated by the participants and it was suggested to conduct such workshops regularly in future.

(Dr Sudhir Rawal, Sr Consulatant & Dr Samir Khanna, Additional Consultant, Department of Genito-Uro Oncology)

Gamma Camera

The strength of nuclear medicine is in its ability to assess tissue functions. There are many aspects of tumor biology that can be usefully evaluated by gamma camera imaging techniques for diagnosis, staging and therapy monitoring. Tumor imaging with radiotracers like ^{99m}Tc-methoxyisobutylisonitrile (MIBI), ^{99m}Tc Tetroformin and ^{201}T1-thallous chloride can achieve good functional results and can be used in places where ^{18}F-FDG is not available.

A new Gamma Camera has been installed in the Department of Nuclear Medicine, RGCI&RC, which was inaugurated by Dr K.V. Swaminathan, Chairman, RGCI&RC on 21st December 2009.

Radionuclide techniques can be used for the detection of skeletal metastasis by scintigraphy most commonly in an oncological setting. Other areas of imaging with ^{99m}Tc based radionuclides include scintimammography (for breast lesions which are difficult to interpret radiologically), sentinel node detection , follow up in brain tumors and assessment of p-glycoprotein mediated multi-drug resistance. Radioactive iodine I^{131} is being used for diagnosis and treatment of thyroid cancer. Many tumors, like endocrine gastro intestinal tumors express somatostatin receptors which can be determined in-vivo by imaging with ^{111}In-octreotide in identifying patients who will benefit from octreotide therapy. Tracers like ^{67}Ga can be used for evaluation of lymphomas and some other malignancies. Conventional radiopharmaceuticals hold lot of promise in the era of PET-CT and can still be used in specific clinical situations in the diagnostic armentarium of patients with various malignancies.

(Reviewed by Dr P S Choudhury, Senior Consultant, Department of Nuclear Medicine)

CASE REPORT FROM RGCI&RC

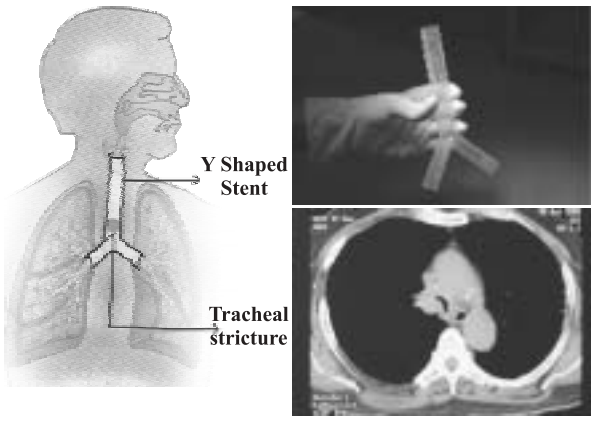
Placement of 'Y - Shaped Stent' for Malignant Tracheal Stricture

Clinical Presentation

A 56 years old male, heavy smoker for 25 years, presented to RGCI&RC with history of repeated episodes of severe respiratory distress associated with loud wheezing since two weeks. He had been diagnosed to have a tracheal tumor at another hospital few months ago, with significantly enlarged mediastinal lymph nodes. The biopsy had revealed a non small cell carcinoma. In view of the advanced disease, he was given chemotherapy. Initially, three cycles of Inj.Gemcitabine with Carboplatin were administered. CT scan showed marginal response. Subsequently, two cycles of Inj. Pemetrexed and Cisplatin were given. The repeat evaluation by CT scan showed significant regression in the tumor as well as in the lymph nodes. However, the CT scan also showed marked stricture formation in the trachea just above the carina. It also showed erosion of the carina, though both bronchi retained their patency. A repeat bronchoscopy confirmed the above findings and it was concluded that the current respiratory distress was due to the tight stricture getting intermittently blocked by secretions. The bronchoscopy showed the stricture was about 1.5 cm above the carina, the carina was badly eroded and the main bronchi on both sides were remarkably unaffected. The previous tracheal tumor had almost completely regressed.

Treatment

In view of the above findings, it was decided to place a Y-shaped silicon Dumon stent in the lower part of the trachea. The limbs of the 'Y-shaped stent' would be inserted into left and right main bronchus while the long stem would remain in the trachea across the stricture. A thorough pre-anesthetic checkup was performed and a high risk informed consent taken in view of the possible complications of bleeding, bronchial tear and respiratory failure. The procedure was performed under intravenous anesthesia with I/V Propafol and Fentanyl. First, a rigid bronchoscope was passed under direct vision with the help of a laryngoscope. Oxygenation was given with a close circuit attached to the bronchoscope. Then, a fibreoptic bronchoscope was passed through the rigid instrument to re-evaluate the stricture, the degree of carinal erosion and the patency of both the main bronchi.



Retained secretions were sucked out and a measurement taken of the right and left main bronchi. The limbs of the Y-stent were cut according to these measurements for proper fitting. *The stent chosen had a long limb diameter of 16mm and length of 6cm and distal limbs of diameter 3.5mm and length 3.5cm left and 2cm right, respectively.* For deployment of the stent in the trachea, it had first to be loaded into an introducer with the help of a specialized applicator. The introducer with the stent was passed into the bronchoscope. From here on, help of an image intensifier was taken to visualize the tip of the bronchoscope which was kept just within the stricture. The stent was pushed through under C-arm guidance with a pusher device. After the stent was released inside, adjustments were made with a rigid forceps to place both limbs in the main bronchi and the long stem across the stricture with the bifurcation against the carina. Perfect placement was confirmed with the fibreoptic bronchoscope.

Follow Up

The patient did very well post procedure. The episodes of respiratory distress completely disappeared and the patient could ambulate without dyspnoea. He was given another cycle of chemotherapy and discharged in a stable condition after a week. He was advised to take regular steam inhalation to avoid mucous impaction in the stent.

This unique procedure performed for the first time in India, is a multi-disciplinary effort by a dedicated team of pulmonologists, namely Dr Rajiv Goyal, Dr Sandeep Nayar, Dr Pratibha Gogia, anesthetists namely, Dr AK Bhargava, Dr BK Naithani and their team, and radiologist Dr Avinash Rao. Dr Sunil Gupta and Dr JB Sharma gave the subsequent chemotherapy.

(Dr Rajiv Goyal, Senior Consultant, Respiratory Medicine)