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From the Desk of Director Research

The "Special Feature" in this issue reports on the Minimally Invasive Surgery in Oncology which is revolutionizing the practice of general surgery and paving the way for scarless treatment. Transrectal High Intensity Focused Ultrasound highlighted under "Perspective" has the potential to become the next generation treatment for primary prostate cancer.

Registries monitoring the cancer burden are an integral part of any cancer control programme and have been covered under "Global Cancer Registries". This issue also profiles "Image Guided Radiotherapy", a new area in the field of radiotherapy with enhanced flexibility and improved outcomes. Other regular features covered are Research and Development, New Technologies, Clinical Trials, Watch Out, Globe Scan and Cancer Control.

Malignant gliomas are the commonest of all adult primary central nervous system tumors and a variety of newer treatments are undergoing development for increasing the survival of these patients. A special gratitude to Dr S Bhaskar, Specialist, Dept. of Neurosurgery, St. Stephens Hospital, Delhi, for contributing the "Guest Article" on Treatment of Malignant Gliomas.

"In Focus" highlights the initiatives and programs of Dr Reddy's Laboratories Ltd which is committed to provide affordable and innovative medicines for healthier lives to people across the world. Our special thanks to Dr Reddy's Laboratories Ltd. for supporting this issue of Cancer News.

The Institute gratefully acknowledges the contributions made by the clinicians, scientists and DNB students of this Institute. Views and suggestions from readers on the Cancer News are welcome.

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

MINIMALLY INVASIVE SURGERY IN ONCOLOGY

Introduction

Minimally invasive approaches have revolutionized the practice of general surgery over the past decade. Since the introduction of fiber-optic endoscopy in the 1960s and the wide spread introduction of laparoscopic cholecystectomy in the 1980s, there has been a huge increase in the use of minimally invasive surgical modalities in clinical practice. The incorporation of these techniques into routine practice has led to the innovation and development of surgical endoscopic techniques in other fields, such as thoracoscopy and transanal endoscopic microsurgery and more recent developments, such as robotic surgery and natural orifice transluminal endoscopic surgery.

However, the introduction of minimally invasive techniques to oncology was met initially with skepticism and controversy because of concerns that such a surgical approach will compromise the oncologic principles of treatment, adequacy of resection of primary tumor and ability to perform a similar extent of lymphadenectomy as compared to an open surgical approach. Early reports pertaining to a incidence of port-site recurrence also created concerns as to the long-term outcome of laparoscopic abdominal cancer procedures. Over the last several years, it has been realized that the incidence of abdominal wall tumor recurrence has not been significant and in fact may be lower than recurrence rates occurring in conventional laparotomy wounds.

Laparoscopic Surgery

Laparoscopic surgery, also called minimally invasive surgery (MIS), bandaid surgery or keyhole surgery, is a modern technique in which operations in the abdomen are performed through small incisions (usually 0.5-1.5cm) as compared to larger incisions needed in traditional surgical procedures. The key element in laparoscopic surgery is the use of a laparoscope. There are two types: a telescopic rod lens system, that is usually connected to a video camera (single chip or three chip) or a digital laparoscope where the charge-coupled device is placed at the end of the laparoscope, eliminating the rod lens system. Also attached is a fiber optic cable system connected to a 'cold' light source (halogen or xenon)

inserted through a 5 mm or 10 mm cannula or trocar to illuminate and view the operative field. The abdomen is usually insufflated with carbon dioxide gas to create a working and viewing space. The abdomen is essentially blown up like a balloon (insufflated), elevating the abdominal wall above the internal organs like a dome. The gas used is CO₂, which is common to the human body and can be absorbed by tissue and removed by the respiratory system. It is also non-flammable, which is important because electrosurgical devices are commonly used in laparoscopic procedures. Laparoscopic procedures are used for evaluating the nature and source of tumors, staging procedures to evaluate the extent of tumors and resection of gastrointestinal and urogynaecological tumors.

Advantages: Minimally invasive surgery results in a shorter hospital stay, a faster recovery, and a faster return to normal activities than traditional surgery. It entails reduced requirement of narcotic analgesia, small skin scars, fewer complications like less trauma to the patient and less blood loss, decreased incidence of ileus, reduced incisional hernia rates, less preoperative pain and less strain. Also, other cancer therapies, like radiation therapy and chemotherapy, can be started sooner after MIS than after traditional surgery.

Disadvantages: (a) Requires special and more expensive equipment, (b) special training required, (c) some procedures take longer time, (d) restricted vision, (e) difficult handling of the instruments, (f) very restricted mobility, (g) difficult hand-eye co-ordination, (h) no tactile perception.

Colon: In 1991, Jacobs and colleagues reported the first laparoscopic resection of sigmoid colon cancer. Since then, experience with laparoscopic techniques for colon resection increased rapidly. Colon cancer is the most notable, with several large prospective multicentre randomized controlled trials demonstrating similar oncologic outcomes with its corresponding open surgical treatment. No other malignancy has had trials of the magnitude of the Clinical Outcomes of Surgical Therapy (COST) and Conventional versus Laparoscopic Assisted Surgery in Colon Cancer (CLASICC) trials to demonstrate the efficacy of minimally invasive treatments to treat cancer.

Esophagus: An initial report by McAnema et al in 1994 described the thoracoscopic assisted mobilization of the esophagus combined with an open abdominal

approach. Since then numerous approaches to minimally invasive esophagectomy (MIE) have been described, including thoracoscopic assisted esophageal resection, laparoscopic transhiatal resection, hand assisted laparoscopic transhiatal resection and three field combined thoracoscopic/laparoscopic resection. There are no randomized trials comparing open and minimally invasive approaches for esophageal cancer; however, reported case series have promising results that suggest that oncologic outcomes after MIE may be similar to those of open series.

Stomach: Endoscopic and laparoscopic resections of benign and low grade lesions, such as gastrointestinal stromal tumors have been received with little controversy and are considered preferred approaches in centres where expertise is available. Currently, a number of MIS options are available for gastric cancer: endoscopic mucosal resection (EMR), intra gastric mucosal resection, laparoscopic wedge resection, partial / total laparoscopic/laparoscopy assisted gastric resections. The first laparoscopic assisted billroth 1 gastrectomy was performed in 1991 as reported by Katano et al for early gastric cancer (EGC). The minimal access approach for gastric cancer was officially approved by the Japanese Gastric Cancer Association in 2001 as procedure of treatment for early gastric cancer.

Although there have been no prospective randomized trials comparing operative and endoscopic resections for early gastric techniques, large retrospective series have identified commonly accepted indications for EMR: well differentiated, intestinal type carcinoma that is limited to the mucosa. Tumors must have no evidence of ulceration and be 20 mm or less in elevated types and 10 mm or less in depressed or flat types. When these criteria are met, and no lymphovascular invasion is seen on final pathologic examination, incidence of lymph node involvement is less than 0.4%. Numerous methods have been used for EMR of EGC, from fulguration to wide excision using a submucosal technique. The benefit of EMR over fulguration is that it provides a complete pathologic specimen for accurate depth staging and does not exclude the possibility of further surgical therapy should the need for it arise. Endoscopic resection techniques include strip biopsy, double snare polypectomy, and cap-fitted endoscopic resection. More recently, the use of endoscopic submucosal dissection techniques has given endoscopists the ability to resect larger cancers as a single specimen, resulting in a higher rate of curative

resection in some series. In addition, intragastric mucosal resection techniques using the transgastric deployment of laparoscopic instruments have been described.

Pancreas: Both laparoscopic distal pancreatectomy and laparoscopic pancreaticoduodenectomy were first reported in 1994 by Gagner. The feasibility of laparoscopic whipples is being supported by recent literature. Various techniques and approaches have been reported including hand assisted, robot assisted as well as using mini laparotomy for reconstruction.

Liver: Since the first report of laparoscopic partial hepatectomy by Gagner et al in 1992, there has been a steady increase in international experience with wedge resection, minor anatomic resections, and even major hepatic resections for both benign and malignant disease. Most commonly, liver resections for malignancy involve resection of either hepatocellular carcinoma (HCC) or metastases from colorectal cancer (CRM). Although there are only a handful of studies examining the oncologic outcomes of laparoscopic hepatic resection for malignancy, early data suggest comparable survival rates to open resections. Intraoperative ultrasound, cavitron ultrasound surgical aspirator (CUSA) and endoscopic linear staplers have made laparoscopic liver resections not only feasible but also beneficial to patients when performed by surgeons with appropriate expertise and experience.

Genitourinary: Laparoscopic radical nephrectomy has become the standard of care for renal cell carcinoma in the majority of institutions during the past decade. The approach to malignant lesions of the adrenal gland is not as straightforward, however. Data suggest that oncologic outcomes after laparoscopic adrenalectomy for primary adrenal cortical carcinoma or metastatic adrenal lesions may be acceptable given appropriate preoperative indications for laparoscopic resection. There does not seem to be a size limitation on laparoscopic resection, as long as adequate local resection and negative margins can be achieved.

Video Assisted Thoracic Surgery (VATS)

First described in early 1990s, the use of VATS for lung cancer has been slow to replace open procedures. The literature shows that VATS has significant advantages with respect to short-term outcomes. Recent results indicate the longer-term oncologic outcomes after VATS lobectomy for early nonsmall cell lung cancer are similar to those after traditional open

resection. Current data support the use of VATS for resection of early stage lung cancer. Studies bring out an immunologic benefit with VATS with improved lymphocyte function and decreased cytokine release.

Video Assisted Thyroidectomy

Video assisted thyroid resection for malignancy has been described in literature but there is no report on long-term oncologic outcome. Techniques described include minimizing incision length to 2.5 to 3.5 cm, video assisted techniques using a small 1.0 to 1.5 cm central or lateral neck incision, and completely endoscopic techniques by means of the chest, breast or axilla (on one or both sides). Lack of long term analyses of survival and recurrence rates should lead to hesitancy in labeling this technique as a definitive oncologic operation. The excellent prognosis and long-term survival is unlikely to be affected by application of MIS in thyroid cancer.

Transanal Endoscopic Microsurgery (TEMS)

TEMS, a technique used as an extension of local transanal excision was developed by Karl Buess in 1980s. The system consists of a 40 mm diameter proctoscope, an optical stereoscope, an insufflation mechanism to create a pneumorectum working space, along with four working ports for instrument access. This results in superior visualization and maneuverability that allows surgeons to access lesions in the rectum that previously were inaccessible with conventional transanal excision techniques. Indication for TEMS in rectal cancer include uT1N0 lesions that are well differentiated to moderately differentiated, with no evidence of lymphovascular invasion. More advanced tumors should not be resected with TEMS for curative intent. However, it can be a feasible option in these patients if significant comorbidities, precluding a major abdominal resection, are present.

Robotic Surgery

Robotic surgery is the use of robots in performing surgery. Three major advances, aided by surgical robots, have been remote surgery, minimally invasive surgery, and unmanned surgery. Major advantages of robotic surgery are precision, miniaturization, smaller incisions, decreased blood loss, less pain, and quicker healing time. Other advantages are articulation beyond normal manipulation and three-dimensional magnification. In 1985, a robot, the PUMA 560, was used to place a needle for a brain biopsy using CT guidance. Further

development of robotic systems was carried out by Intuitive Surgical with the introduction of the da Vinci Surgical System and Computer Motion with the AESOP and the ZEUS robotic surgical system.

The da Vinci Surgical System comprises three components: a surgeon's console, a patient-side robotic cart with 4 arms manipulated by the surgeon (one to control the camera and three to manipulate instruments) and a high-definition 3D vision system. Articulating surgical instruments are mounted on the robotic arms which are introduced into the body through cannulas. The surgeon's hand movements are scaled and filtered to eliminate hand tremor and then translated into micro-movements of the proprietary instruments. The camera used in the system provides a true stereoscopic picture transmitted to a surgeon's console. The da Vinci System has FDA clearance for a variety of surgical procedures, including surgery for prostate cancer, robot assisted hysterectomies and cancer staging.

Future Perspective

The era is rapidly approaching when flexible endoscopy alone may be used through "natural orifices" to remove malignant lesions without transgressing the abdominal cavity. Potential advantages of *Natural Orifice Transluminal Endoscopic Surgery (NOTES)* include lower anesthesia requirements; faster recovery and shorter hospital stays; avoidance of the potential complications of transabdominal wound infections (e.g. hernias); less immunosuppression; better postoperative pulmonary and diaphragmatic function; and the potential for "scarless" abdominal surgery. Critics challenge the safety and advantages of this technique in the face of effective minimally invasive surgical options, such as laparoscopic surgery.

It is important to continue to apply good science to these futuristic applications in the form of randomized controlled trial and guideline development to avoid the pitfalls associated with application of inappropriate oncologic principles. Continued randomized prospective trials developed by recognized trial groups are mandatory to answer the pertinent questions posed by newer and more aggressive minimal access approaches.

(Reviewed by Dr Veda Padam Priya, DNB Student, Dr Pankaj Pande, Consultant & Dr Kapil Kumar, Senior Consultant, Dept of Surgical Oncology)

GUEST ARTICLE

TREATMENT OF MALIGNANT GLIOMAS

Introduction

Primary malignant brain tumors though account for only 2% of all the adult cancers, but the related morbidity and mortality is very high. The annual incidence of primary malignant brain tumor from 1997 to 2001 was 7.3 per 100,000 person years. Of all adult primary central nervous system tumors, glioblastoma multiforme (GBM) is the commonest and there are about 7,000 to 8,000 new cases diagnosed annually in the USA. The median survival of patients with GBM is 9 to 12 months. The majority of patients die from this disease within 2 years, and less than 5% survive 5 years. Young age and good Karnofsky performance status (KPS) have been identified as major prognostic factors in GBM. There has been only a modest increase in the survival of these patients despite newer and advanced treatment strategies.

Current Therapeutic Modalities

Surgery: Most high grade gliomas are surgically resected as widely as possible without significantly increasing the neurological deficits, followed by chemo-radiotherapy. If feasible, surgical resection should include the contrast enhancing tumor as seen on a Magnetic Resonance Imaging. Surgery offers benefits by reducing mass effect and tumor volume resulting in better effect for adjuvant modalities by removing the necrotic core, which may be a reason for failure of chemotherapy. Surgery has been shown to improve outcome when done prior to chemotherapy and radiotherapy. Median survival increased from 17 weeks to 37.5 weeks in patients treated with postoperative whole brain radiotherapy (WBRT).

Radiotherapy: Randomized studies have shown that 50 to 60 Gy of WBRT following surgery has increased the median survival of patients with GBM from 14 to 36 weeks. Partial brain radiation is the norm as there is no benefit of WBRT in terms of survival or local control, since 90% of the recurrences occur within 2 cms of the known primary tumor. Newer techniques like focal beam RT, termed involved field RT (IFRT), have maximized the dose to the tumor while minimizing the radiation to the normal tissue. These include intensity modulated RT (IMRT) and 3D-conformal RT. IMRT is particularly advantageous when radiation-sensitive

structures close to the target area are least affected. Radiosurgery can be done with x-rays produced by linear accelerators, or gamma rays produced by Co⁶⁰ and charged particles as protons produced by cyclotrons. Stereotactic radiosurgery (SRS) administers external radiation via multiple convergent beams to a discrete tumor volume. A few small studies have shown some benefits in giving SRS after standard therapy of GBM but no randomized trials have been done to date. Interstitial brachytherapy, where radioisotope seeds are placed into the tumor or resection cavity, delivers a large radiation dose to the tumor volume with rapid fall-off in the surrounding tissues. Despite the advantages, this modality has shown very marginal improvements in the outcome. The University of California, San Francisco, was able to show a benefit from brachytherapy by the addition of hyperthermia. Hyperthermia additionally kills cells by targeting cells in the S-phase, which are resistant to radiation but sensitive to heat. Hyperthermia inhibits sublethal repair and improves reoxygenation, thus improving the results of radiation.

Chemotherapy: Chemotherapy had not shown any significant results in malignant gliomas till the advent of temozolamide (TMZ). TMZ, an oral alkylating agent, is the drug of choice in high grade gliomas for concurrent and adjuvant therapy. It has been proved in a trial that TMZ increased progression-free survival (6.9 versus 5 months without TMZ), overall survival (14.6 versus 12.1 months) and two-year survival (26 versus 10%). In spite of these good results, resistance to treatment remains an obstacle. O(6)-alkylguanine-DNA alkyltransferase is a DNA repair protein coded by the (6)-methylguanine-DNA methyltransferase (MGMT) gene on chromosome 10. It reverses the cytotoxic lesion created in the DNA by TMZ and nitrosourea by removing the alkyl groups from the O(6) position of guanine. MGMT depletion would increase the cytotoxic effects of these agents but associated myelosuppression has led to the abandonment of this combined strategy. Gliadel wafers contain carmustine (BCNU) embedded in a biodegradable matrix, which is designed to release the agent over a two-to three-week period. Patients receiving carmustine polymer had a statistically significant increase in median survival (13.9 versus 11.6 months).

Newer Therapeutic Modalities

Signal Transduction Inhibitors: Epidermal growth factor receptor (EGFR) is found to be amplified and over

expressed in approximately half of the glioblastomas. Inhibition of tyrosine kinases and associated growth factor pathways were the main foci of targeted molecular therapies in GBM. Gefitinib (Iressa) is a selective, small-molecule inhibitor of the EGFR. Erlotinib (Tarceva) is another one which also inhibits the active mutant EGFRvIII found in around 40% of GBMs. Newer dual tyrosine kinase inhibitors like lapatinib (GW 5720160) and AEE788 are undergoing clinical trials. Compounds which inhibit platelet derived growth factor receptor are also being investigated for the treatment of high grade gliomas. Imatinib mesylate has been seen to enhance the cytotoxic effects of ionizing radiation in a human GBM cell line.

Anti-Angiogenesis Agents: Targeting factors and pathways actively participating in angiogenesis is a potential effective approach. In conventional chemotherapy, the blood brain barrier is an obstacle whereas the endothelial cell is the primary target in anti-angiogenic therapy. These cells are in direct contact with the blood, so anti-angiogenic compounds reach their target much easier than conventional chemotherapy. Being genetically more stable, these endothelial cells are less likely to develop resistance. The cytostatic nature of this therapy necessitates life-long maintenance treatment. Angiogenesis depends on multiple pathways, so combination of anti-angiogenic therapies may be required. A combination of bevacizumab (monoclonal antibody that binds vascular endothelial growth factor) and irinotecan (potent topoisomerase inhibitor) has shown promising results.

Immunotherapy: This includes adoptive immunotherapy (passive administration of sensitized immune cells, mostly abandoned in recent years), passive immunotherapy (target specific exogenous antibodies) and active immunotherapy with vaccines. Passive immunotherapy includes use of radioactive iodine-labeled monoclonal antibodies to tenascin (an extracellular matrix protein) being delivered to the tumor resection cavity. Active immunotherapy makes use of dendritic cells which are potent antigen-presenting cells that are loaded with tumor lysates or peptides. Attempts have also been made to vaccinate the immune system and recognize the EGFR vIII variant, even though only 30-40% of patients may express this variant.

Gene Therapy: Herpes simplex virus-thymidine kinase gene therapy has been used most commonly in genetic therapy. Gene therapy has been done by direct delivery

methods, involving either stereotactic intratumoral injection or intraoperative injection into the margins of the tumor cavity. The commonest vehicles are the adenoviral particles. The disadvantages of gene therapy include low tumoricidal effect in situ and a limited distribution of transgenes and/or vectors to tumor cells, localized peripherally from the main tumor mass. Also, virus derived vectors may cause immune mediated toxicity by antibodies.

Convection Enhanced Delivery (CED): This is one way to overcome the blood brain barrier and achieve therapeutic concentrations within the parenchyma on a regional basis. The parameters which affect the distribution of the solutes are infusion rate, cannula size, infusion volume, interstitial fluid pressure and tumor tissue structure. A phase 1 trial of topotecan (topoisomerase inhibitor) delivered by CED has shown promising results. Preliminary results have shown that survival advantage is more than in historical recurrent malignant gliomas. Another newer modality being investigated in the laboratory is the targeted delivery of controlled-release nanoparticles to high grade gliomas using contrast agent microbubbles and high intensity focused ultrasound.

Conclusion

In spite of the advances in the understanding of biology of malignant gliomas, survival rates have improved only marginally. Surgery and adjuvant chemoradiotherapy are the standard treatments for high grade gliomas and a variety of newer treatments are undergoing development which hold promise for increasing the survival of these patients. Better histological and biological understanding of the molecular basis of tumorigenesis will allow for the development of newer targeted therapies. It will also help in selecting patients who will be better candidates for adjuvant therapies.

Suggested Readings

1. Grossman SA, Batara JF: Current management of glioblastoma multiforme. *Semin Oncol*; 2004;31; 635-44.
2. Omay SB, Vogelbaum MA: Current concepts and newer developments in the treatment of malignant gliomas. *Indian Journal of Cancer*; 2009;46;88-95.
3. Sathornsumetee S, Rich JN: Newer approaches to primary brain tumor treatment. *Anticancer Drugs*; 2006;17;1003-16.

(Dr S Bhaskar, Specialist, Dept of Neurosurgery, St. Stephens Hospital, Delhi)

PERSPECTIVE

TRANSRECTAL HIFU

Introduction

High Intensity Focused Ultrasound (HIFU) is a novel emerging therapeutic modality that uses ultrasound (US) waves, propagated through tissue media, as carriers of energy. It uses energy focused to a specific point within the prostate, thus enabling targeted destruction of prostatic tissue. HIFU therapy for localized prostate cancer has been widely accepted in Europe and Asia. Approximately 13,000 men have been treated till date with HIFU worldwide.

Indications

For the majority of patients, the goal of HIFU therapy is curative. Any patient with organ-confined prostate cancer may be a primary candidate. HIFU can treat the entire prostate capsule and beyond, if there is no capsular invasion and if the neurovascular bundles are not involved, the nerves can be spared, and potency maintained. Early seminal vesicle invasion can be treated with HIFU. The best candidates for curative intent are clinical/pathological stages T1c-T3. Aside from primary therapy, HIFU can be utilized as salvage therapy, primarily after radiation or radical prostatectomy. If there is local recurrence after radical prostatectomy, HIFU can be used to treat that lesion. HIFU can also be used for palliative therapy, debulking large symptomatic tumors that are causing pain, bleeding and obstruction.

Contraindications

Glands with extensive or very large calcifications will interrupt, block and reflect the HIFU beam, so these glands cannot currently be treated. Rectal stenosis that does not allow the probe to be placed, HIFU cannot be used. A history of rectal fistula is also a current contraindication.

Procedure

HIFU is performed as an outpatient procedure, usually under epidural anesthesia or GA with patient in dorsal lithotomy position (Sonablate® unit). The HIFU probe is then placed into the rectum and multiple gland images are taken. All of the images are reviewed and the treatment zones are defined and logged into the treatment computer. Absorption of ultrasound energy creates an increase in temperature which causes coagulation of tissues within the focal area. A cooling balloon surrounding

the probe protects the rectal mucosa from high temperature. The entire procedure takes around 90 min depending on the gland size (average time 2-3 h). After the procedure, urethral catheter is placed for one to two weeks. For bigger gland size, TURP or androgen blocking is done for three to six months for downsizing.

Risks and Complications

Immediately after surgery, there will be urinary retention which can be reduced by Preoperative TURP. Rectal injury appears to be no longer a significant concern for HIFU. Reported rectal fistula with newer technology is 0.5%. Incontinence is extremely rare and the potency after HIFU can be good in comparison to other techniques.

Results of Clinical Studies

The HIFU series with the longest follow-up is reported by the University of Regensburg in Germany covering 163 patients with clinical stage T1-T2N0M0, biopsy proven, localized prostate cancer with a serum prostate specific antigen (PSA) level of ≤ 20 ng/mL, Gleason score of ≤ 7 , treated with HIFU. Median follow-up was 4.8 years. Of the 163 patients, 86.4% achieved a PSA nadir of < 1 ng/mL and 92.7% had negative post-treatment biopsy findings. Biochemical recurrence free survival rate at 5 years was 75%, with salvage treatment initiated for 12% of the patients. On multivariate analysis, the pretreatment PSA level was the only statistically significant predictive factor of recurrence ($P = 0.005$). In another study by Uchida published in October 2005, biochemical disease-free survival rates in patients with serum PSA < 10 ng/ml and 10-20 ng/ml were 75% and 78% ($P = 0.6152$). No viable tumor cells were noted in 68% of patients by postoperative prostate needle biopsy.

Conclusion

HIFU is a novel therapeutic modality for prostate cancer treatment. The control and precision that HIFU provides, truly allows the surgeon to precisely ablate the prostate gland with pinpoint accuracy and thereby preserve the adjacent structures. Furthermore, because HIFU is non-ionizing, there is no collateral tissue damage. Many European centers are performing prostate incisions or TURPs prior to HIFU in an attempt to alleviate development of obstruction. HIFU has the potential to become the next generation treatment for primary prostate cancer.

(Reviewed by Dr Sanjay Mittal, Clinical Assistant and Dr Sudhir Rawal, Senior Consultant, Dept of Genito Uro-Oncology)

CANCER REGISTRIES

Introduction

Each year, more than 10 million new cancers are diagnosed worldwide and 6 million patients suffer a cancer-related death. Cancer registration is an indispensable instrument in cancer control programmes. Initially these programmes were concerned primarily with describing cancer patterns and trends, but later, many were able to follow up the registered patients and calculate the survival. In the last 20 years, the role of registries has expanded further to cover the planning and evaluation of cancer control activities and the care of individual cancer patients. In 1966, the results of 32 registries were reported in volume 1 of "Cancer Incidence in Five Continents". Forty years later, there were 449 member registries of the International Association of Cancer Registries, covering 21% of the world population.

A cancer register is designed to collect information about the occurrence (incidence) of cancer, their locations (topography) within the body, the types of cancers (histology) that occur, extent of cancer at the time of diagnosis (disease stage) and the treatment the patients receive. There are two types of cancer registries: population-based cancer registries (PBCR), and hospital-based cancer registries (HBCR), which differ in their methods and aims. Their data can be used in a wide variety of areas, such as epidemiological research, descriptive studies, analytical studies, healthcare planning and monitoring, patient care, survival and screening. The data is also used by individual hospitals for comparison with the national standards to identify areas for quality improvement. International collaboration and knowledge sharing is indispensable for development and improvement of cancer registration worldwide. Global standardization of registry data collection and reporting will eventually have a profound effect on the management and outcome of cancer.

Growth Graph

Collection of data to chart trends in cancer incidence began in early 1900. Some of the cancer registries around the world are in Hamburg (1927), New York (1940), Connecticut (1941), Denmark (1942), Japan (1951), UK (1958), SEER of US (1973),

NCRP-India (1981), National Cancer Data Base of US (1989), Australia (1986), European network of cancer registries (1989), China (1990), NCRP of US (1992), Canadian Cancer Registry (1992), GLOBOCAN (2002), etc.

Because of the emerging importance of cancer as a health problem for developing countries, World Health Organization (WHO) has promoted the development of national cancer control plans, in which the role of cancer registries is well defined. A WHO subcommittee on the "Registration of Cases of Cancer" was set up in 1950 that provided the first set of methodological guidelines for cancer registration. At the International Symposium on Geographic Pathology and Demography of Cancer, arranged by the International Union Against Cancer in 1950, the need for enumeration of all new cases of cancer in a defined geographic area was emphasized.

In 1956, The American College of Surgeons required hospitals to have a cancer registry.

The International Agency for Research on Cancer (IARC) was established in May 1965. A major goal of IARC is the identification of causes of cancer so that preventive measures may be adopted. Cancer Mondial Website provides access to information on the occurrence of cancer worldwide and is managed by the Descriptive Epidemiology Groups of IARC. This site is based on original data collected by PBCR sent to cancer epidemiology and cancer control wing of IARC.

The International Association of Cancer Registries (IACR) was founded in 1966 as a professional society to foster the exchange of information between cancer registries internationally, improve quality of data and comparability between registries. It is primarily for PBCRs, which collect information on the occurrence and outcome of cancer in defined population groups. To encourage comparisons between different registries, countries, and over time, the IACR has developed registry practices and standard definitions for collecting, coding and presenting data. Center for Diseases Control and Prevention (CDC) provides funds to support IACR's annual conference, which is consistent with CDC's mission to support PBCRs worldwide. IACR has official alliance with WHO since January 1979.

The World Cancer Declaration issued at the UICC World Cancer Congress 2006, requires increasing the number of countries with viable and adequately funded

cancer surveillance system, including cancer registries. These systems should collect and analyze data on the magnitude of cancer burden and its likely future evaluation, prevalence and trends in risk factors, mortality, person-years of life lost and survival, and monitor the effects of prevention, early detection/screening, treatment and palliative care.

Cancer Registry in India

The National Cancer Registry Programme (NCRP) is a long-term activity of the Division of Non-Communicable Diseases of the Indian Council of Medical Research (ICMR). ICMR initiated the NCRP in 1981 and commenced a network of cancer registries across the country that started functioning from January 1982. Three HBCRs were commenced at Assam Medical College, Dibrugarh; Regional Cancer Centre, Thiruvanthapuram; and Post Graduate Institute of Medical Education and Research, Chandigarh. Over the years, many HBCRs and PBCRs have been initiated.

Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC) has its own HBCR system which includes data on geographical distribution of cases, magnitude of cancer load, sex ratio of common cancers, site-wise age distribution of cancers in both sexes and much more. RGCI&RC data pertaining to Delhi is also being submitted to the Delhi Cancer Registry. A total of 93075 patients were registered at RGCI & RC from July 1996 to December 2007. Out of these, 60267 cases were found to be confirmed cases of cancer. Since the year 2006, RGCI&RC is participating in a project under the NCRP. An "online data reporting system" exists under NCRP and RGCI&RC is using the online submission facility for the cancer of breast, cervix and head & neck. Special software has been developed for maintaining the records of cancer registry and Electronic Medical Records System is expected in the Institute in 2009.

Benefits of Cancer Registries

Physicians require the data to learn about risk factors and the natural history of disease with a view to identifying cancer earlier. These data allow to estimate cancer risk and incidence by geographic locations, socio-economic status and the country's level of industrialization. Comparing global data overtime also allows assessment of changes in incidence, risk factors, diagnosis and treatment. Data from different countries can be compared to assess different patient

subgroups. Such information is critical to advancing our understanding of difficult-to-treat malignancies which otherwise would be impossible without multinational data from cancer registries.

Cancer registration is also important in planning cancer initiatives and allocating resources. National-specific incidence and mortality data can assist countries in prioritizing their cancer health policy. Cancer registries are the basis for these decisions and allow for the effectiveness of limited resources to be maximized. The opportunity to track changes overtime and compare results in other countries is invaluable. Population-based data is demanded by both patients and clinicians to make lifestyle and cancer care decisions.

Obstacles to Cancer Registries

The following issues make worldwide implementation and interoperability challenging. Firstly, there is universal concern regarding the quality of the data reported, particularly in the developing world. Secondly, each registry collects a different set of variables, thus making integration of multiple cancer registries a challenging task. Thirdly, efforts are often duplicated by cancer registries serving similar populations. It is necessary to overcome cultural stigmas associated with the diagnosis and reporting of cancer.

The problems involved in collecting and analysing cancer registry data in developing countries are lack of basic health services; the stability of the population, identity of individuals; trained personal; follow up, nonavailability of census data; data-processing facilities and confidentiality. Limited funding for considerable technological infrastructure design and registry software is an issue in the developing countries.

Conclusion

Registries are an integral part of any cancer control programme for assessing and monitoring the cancer burden. An effective, organized and collaborative worldwide effort for cancer registration is needed. Bringing together data from around the globe will undoubtedly improve the understanding of cancer. Assuming that all established, maturing and newly formed registries can work together is of critical importance as we move ahead with global cancer registration. Global cancer registration can help in understanding the disease better and use the available resources to maximize prevention, diagnosis and treatment interventions.

IN FOCUS

DR REDDY'S LABORATORIES LIMITED

Dr Reddy's Laboratories has stepped into the 25th year of its existence since Dr K Anji Reddy started it with an initial capital of Rs 25 lacs in 1984 as a predominantly bulk drug selling company. It has been an eventful journey. Though still of just 25 years, Dr Reddy's Lab gets the accolade for building a culture as strong as that of a 100 years old company.

A strong portfolio of businesses, geographies and products gives Dr Reddy's an edge in an increasingly competitive global market and allows it to provide affordable medication to people across the world, regardless of geographic and socio-economic barriers. Dr Reddy's is committed to provide affordable and innovative medicines for healthier lives.

Dr Reddy's was the first company to come up with a biosimilar filgastim "Grafeel" and then again repeated history by making world's first biosimilar monoclonal antibody "Reditux". These products have added to the incredible faith and reputation of the company and at the same time has given a significant boost to the oncology business of Dr Reddy's. Oncology India is one of the major divisions of Dr Reddy's which has made a major mark not just by fulfilling its business purpose but also by being sensitive to the fact that cancer care cost can be really debilitating for the patients and hence bringing free drug assistance for the patients through its program called SPARSH. Its other initiatives like Promotion of Oncology Training and Education in India (PromOTE India) in collaboration with Indian Co-operative Oncology Network has earned all-across appreciation. Aim of PromOTE India is to bridge the gap between the oncologists and general physicians in understanding the patients needs and facilitating treatment in a much better way.

Dr Reddy's Foundation for Health Education (DRFHE) is another initiative by Dr Reddy's Laboratories which is complementing the business purpose of the organization in all means. Since its inception, DRFHE has created value-adding Corporate Social Responsibility (CSR) initiatives that develop qualified professionals to complement the existing healthcare system through an integrated approach to good health. In this, DRFHE endeavours to go beyond the traditional 'charity-centric'

definition of CSR by adding value to both the healthcare system and society as a whole.

There are many other DRFHE activities which are making a huge difference. The Inner Circle is a program for young doctors that aims to develop in them the business and soft skills required for development of a successful career in medicine. The 'Abhilasha' program for nurses is structured to give them the skills necessary for effective patient management and enhanced service orientation. 'Sarathi' targets physicians' assistants, and helps these assistants enhance their medical knowledge, personal effectiveness and interpersonal skills so that they, in turn, can help the patients better. "Sanjeevani" is a program designed for the pharmacists to ensure that they develop self confidence and empathy towards their customers and improve various skills required in effective prescription dispensation.

At Dr Reddy's, sustainability is a multi-dimensional aspiration, which has its roots in the very purpose of its existence-providing affordable medicines to people around the world and meeting unmet medical needs through innovation. Its business, by its very nature, serves a social good, so it has a far deeper reason than profits alone to drive its performance. Its commitment to environment is the driving force for achieving sustainability. They measure the environmental impact of its operations through certain key parameters like water consumption, effluent discharge, COD and TDS and load discharge. Five units of its API plants, out of six, have achieved Zero Discharge status.

Other initiatives like Naandi and Livelihood Advancement Business School (LABS) have made an indelible mark in their respective work areas. Naandi, which in Sanskrit means a new beginning, is one of the largest and fastest growing social sector organisations in India working to make poverty a history. Founded in 1998, their work has three broad sectors: Child Rights, Safe Drinking Water and Sustainable Livelihoods. The LABS, another flagship program of Dr Reddy's Foundation, has made significant progress. In 2004-05, it created 25,000 livelihoods, taking the total to 35,000 so far. LABS has certainly come a long way since 1996, when it initiated the 'Micro Entrepreneur in Sanitation' Program in Hyderabad.

Dr Reddy's continues to make an impact in the society through its programs.

(Provided by Dr Reddy's Laboratories Ltd)

RESEARCH AND DEVELOPMENT

Breast Cancer Stem Cells

Cancer stem cells are a small but important component of circulating and disseminating tumor cells. Researchers from M.D. Anderson Cancer Center conducted the first prospective study to investigate the presence of breast cancer stem cells of primary breast cancer patients. They found that breast cancer patients who received chemotherapy prior to surgery had heightened levels of cancer initiating stem cells in their bone marrow and the level of such cells correlated to a tumor's lymph node involvement. The research showed a higher presence of cancer stem cells correlated with more advanced disease, suggesting that they may one day be a prognostic factor for identifying those at greatest risk of metastasis and cancer. The results suggest the need for additional biological therapies as well as a potential and promising new direction for the study of micro-metastasis. The research also presents a strong case for obtaining bone marrow specimens from locally advanced breast cancer patients undergoing surgery after neo-adjuvant therapy with the rationale that it will lead to better monitoring of patients who may need additional treatment.

(M.D. Anderson Cancer Center, May 21, 2009)

Cotara® for Brain Cancer

Peregrine Pharmaceuticals Inc's Cotara®, an experimental treatment for brain cancer, links a radioactive isotope to a targeted monoclonal antibody designed to bind to the DNA histone complex that is exposed by dead and dying cells found at the center of solid tumors. The mechanism delivers its radioactive payload to the adjacent living tumor cells and destroys the tumors from the inside out with minimal radiation exposure to healthy tissue. Cotara® is delivered using convection-enhanced delivery that targets the specific tumor site in the brain. In a previous clinical study, a subset of patients with recurrent glioblastoma treated with Cotara® achieved a median survival of 38 weeks and in the present study, 25% of 28 recurrent patients survived for more than a year post-treatment and 10% of patients survived for more than three years. This drug has been granted orphan drug status and fast track designation for the treatment of glioblastoma multiforme (GBM) and anaplastic astrocytoma by the US FDA. A phase 1 dosimetry trial in GBM patients in the US has

completed patient enrolment and a phase II safety and efficacy trial on GBM patients in India is going on.

(Peregrine Pharmaceuticals, Inc., May 29, 2009)

Marker for Colorectal Cancer

A research team investigated the association between TSPAN1, a tumor-related gene and human colorectal adenocarcinoma. In this study, total RNA was extracted in 20 human adenocarcinoma tissues by TSPAN1 mRNA assay by RT-PCR. Eighty-eight specimens of human colorectal adenocarcinoma were surgically removed. TSPAN1 protein levels in cancer tissues were determined by immunohistochemistry using a polyclonal antibody against self-prepared TSPAN1. Results indicated that TSPAN1 protein expression in colorectal cancer tissue significantly correlated with the histological grade, cell expression PCNA, lymph nodal metastasis and TNM staging of the disease. Patients with TSPAN1 protein overexpression had a significantly shorter survival period than those in patients with TSPAN1 protein negative or weak expression, respectively. By multivariate analysis, TSPAN1 protein expression demonstrated an independent prognostic factor for human colorectal cancers. The results showed that testing TSPAN1 expression in tissues would be a useful tool to evaluate the prognosis of patients with colorectal cancer.

(World J Gastroenterol, May 14, 2009)

Novel Therapy for Cancer

A recent study has shown that a common anti-viral drug, ribavirin, can be beneficial in the treatment of cancer patients as it suppresses the activities of the eIF4E gene in patients. This gene is dysregulated in 30% of cancers, including breast, prostate, head & neck, colon and stomach cancer. The researchers found that ribavirin blocks eIF4E with no side effects on patients. M4/M5 acute myeloid leukemia patients were studied who had undergone several other treatments that had previously failed. They observed clinical improvements with even partial and complete remissions. Trials in the near future are planned to overcome the resistance that develops over time to ribavirin and the researchers are looking forward to more complete remission. According to them combination therapy with chemotherapeutic agents may enhance the efficacy of this treatment. They hope to test whether ribavirin is as effective in the treatment of other cancers with dysregulated eIF4F.

(Blood, May 9, 2009)

NEW TECHNOLOGIES

DIAGNOSTICS

Prostate Cancer Screening

The six-gene molecular diagnostic test, when combined with a prostate-specific antigen (PSA), accurately detected prostate cancer more than 90 % of the time. Earlier studies suggest that the conventional PSA test is 60-70% accurate in detecting cancer. Men who are found to have elevated levels of PSA in routine screening tests are often referred for a biopsy of the gland to check for tumors. Nearly two-thirds of biopsies performed do not find any cancerous cells, which underscores the need for a more accurate method for detecting prostate cancer. Researchers sought to measure the accuracy of a six-gene whole blood RNA transcript based diagnostic test both in terms of its sensitivity and specificity. The study found that the six-gene model was more accurate than PSA alone at predicting cancer if one had it and no cancer if one did not. The test's accuracy improved even more when PSA measurements were added. Thus, the new test could eliminate tens of thousands of unnecessary, painful and costly prostate biopsies annually.

(Dana-Farber Cancer Institute, May 29, 2009)

Tests for Breast Cancer Subtypes

According to the breast cancer molecular subtyping by gene expression profiling, there are five breast cancer subtypes. However, there is no simple immunohistochemical (IHC) test available to distinguish two most common subtypes luminal A and B. The study conducted by researchers showed that a panel of four IHC tests, including estrogen and progesterone receptor expression, Ki67 expression and HER2 status, could distinguish luminal A and B breast cancer subtypes. They subtyped 357 breast tumors by gene expression profiling and tested them for Ki67 expression by IHC to determine a cut point that distinguished between luminal A and B tumors. They then examined 2,847 independent breast tumors with four IHC tests. They found that Ki67 was expressed in 13% or less of the cells in luminal A tumors. Using that cut point for Ki67 expression, the four IHC tests could distinguish between luminal A and B subtypes in the independent series of breast cancers.

(Journal of National Cancer Instt, May 12, 2009)

EQUIPMENTS

Microwaves to Destroy Liver Tumors

Most patients with liver cancer are deemed inoperable but with the development of pioneering technique using microwaves, thousands of patients worldwide could be offered curative treatment, even if they have established liver cirrhosis. The treatment of more than 100 patients with liver cancer has resulted in curing or extending life for many of them, whose life prognosis was less than twelve months. More than one third of the patients treated are still alive after three years and some have been, quite simply, pronounced cured and discharged. The earliest patient to be discharged was a trial patient treated nine years ago. Several more are alive and well five years after receiving treatment. The advantages over other machines designed to destroy tumors are that it is quick and produces cancer cell death with very few side effects. Only the tissue in the immediate field of the microwave energy is destroyed and not in other parts of the body. Large tumors, up to 6-8 cms in diameter, can be treated within 4-6 minutes. The system is safe, fast, reproducible and a very powerful device.

(University of Leicester, May 14, 2009)

New Device that Tracks Radiation

Increasing cancer cure rates and decreasing complications associated with radiation therapy are the goals physicians strive for when treating their patients. DVS® (Dose Verification System) is the first wireless, implantable, as small as the length of a dime, radiation sensor available in the United States to assist physicians in obtaining these goals. The sensor provides data on the precise amount of radiation being delivered to the tumor and surrounding normal tissue. The first DVS® sensor was inserted inside the patient's tumor bed in less than 15 minutes, which transmitted the radiation dose information to a hand-held monitor during each of the daily treatments. DVS® enables the doctors to verify that the patient is receiving the prescribed dose. If a dose deviation is detected, the treatment plan can be modified and corrected for each individual patient. Traditional radiation therapies rely on knowing the exact location of the tumor, but provide no guidance on quantifying the actual dose being delivered to the tumor. DVS® offers an unprecedented level of precision to physicians and added reassurance to breast and prostate cancer patients.

(Maury Regional Medical Center, May 19, 2009)

TECHNIQUES

Breakthrough in Radiotherapy

Real-time image-guided radiotherapy, combining radiation treatment with non-invasive magnetic resonance (MR) imaging, would be far less harmful for patients as it would leave less healthy tissues damaged and give radiation oncologists the possibility of instantly modifying the treatment dose as tumors change in size and shift. The findings of the University Medical Centre Utrecht, the Netherlands, have successfully proved that simultaneous radiation treatment and diagnostic-quality MRI are feasible. By actively shielding the radiation beam from the MRI scanner's magnet and redesigning the treatment room setup, which has until now been difficult to put into practice, the researchers have managed to produce high quality, real-time MRI images, which could enable oncologists to target radiation far more accurately while it is being applied. Working towards a clinical prototype, the research team is hoping to start the first clinical test in a year's time.

(Biocompare News, May 20, 2009)

Total Mesometrial Resection

Total mesometrial resection (TMMR) is a modified version of the traditional radical hysterectomy, which could allow surgeons to perform a radical hysterectomy in patients with early-stage cervical cancer with fewer complications, reduced morbidity and a lower risk of local tumor recurrence than current surgical methods. TMMR involves more accurate, anatomically based resection of the cancer to prevent damage to pelvic autonomic nervous system and minimise surgical trauma. Radical hysterectomy has a relatively high rate of tumor recurrence and many patients experience postoperative bladder and bowel dysfunction because of damage to the autonomic nerve system.

Researchers at the University of Leipzig, Germany, have assessed the effectiveness of TMMR without radiotherapy in 212 patients with early-stage cervical cancer. Overall, findings showed recurrence-free survival of 94% and 5-year survival of 96% with low treatment-related disease. At a median follow-up of 41 months, only 10 patients had a recurrence of their cancer. TMMR without adjuvant radiation has the potential to improve survival by 15-20%. Further evaluation of the technique with multi-institutional controlled trials is suggested.

(The Lancet Oncology, July, 2009)

DRUGS

BiovaxID® Vaccine

BiovaxID® is a personalized, patient-specific therapeutic vaccine designed to stimulate patient's own immune system to recognize and destroy cancerous B-cells that may remain in body or may arise after the patient has been treated with chemotherapy. Unlike other approaches to treating Non-Hodgkin's lymphoma (NHL), BiovaxID® kills only cancerous B-cells with initial indication of follicular NHL. Eight years pivotal, randomized, multi-center, double-blind, controlled phase III trial has shown that BiovaxID® significantly prolonged disease-free survival in follicular NHL. It is a safe and well-tolerated vaccine, administered as a subcutaneous injection along with granulocyte-macrophage colony-stimulating factor and keyhole limpet hemocyanin, which together enhance potency of immune response induced by BiovaxID®. It is anticipated that BiovaxID® could be used to treat mantle cell lymphoma, chronic lymphocytic leukemia and multiple myeloma.

(Biovest International, Inc, June 2, 2009)

Sprycel® for Chronic Myeloid Leukemia

The US FDA has granted full approval for Sprycel® (dasatinib) for treatment of adults in all phases of chronic myeloid leukemia (CML) (chronic, accelerated or myeloid or lymphoid blast phase) with resistance/intolerance to prior therapy, including Gleevec (imatinib mesylate). This is based in part on results from a phase III randomized, open-label, dose-optimization study on chronic phase CML patients with resistance/intolerance to Gleevec. A total of 167 patients who received Sprycel® 100 mg once daily, showed 80% progression-free survival rate estimated at 2 years, 91% overall survival rate estimated at 2 years, 63% of patients achieved major cytogenic response (MCyR) at 22 months, 93% of patients who achieved MCyR maintained that response for 18 months.

Sprycel® fulfills a need for second-line treatments for CML patients with resistance/intolerance to Gleevec and 2-year follow-up data support its use as a treatment option for this patient population. Approved label now includes a new recommended starting dose of Sprycel® 140mg once daily for accelerated, myeloid blast and lymphoid blast phase CML resistant/intolerant to prior therapy, including Gleevec and Ph+ALL resistant/intolerant to prior therapy.

(Bristol-Myers Squibb, May 27, 2009)

CLINICAL TRIALS

Combination Chemotherapy Drugs

Researchers conducted a phase III clinical trial among 324 patients with inoperable advanced biliary tract cancer, in which participants were assigned to receive chemotherapy with Gemzar® alone or Gemzar® plus cisplatin. Information from this trial was combined with information from a prior phase II trial, bringing the total number of participants to 410. Researchers noted that adding cisplatin to Gemzar® therapy significantly slowed cancer progression and extended survival for these rare but hard to treat cancers. Overall survival was 11.7 months among patients treated with Gemzar® plus cisplatin compared with 8.3 months among patients treated with Gemzar® alone. Survival without cancer progression was 8.5 months among patients treated with Gemzar® plus cisplatin compared with 6.5 months among patients treated with Gemzar® alone. This is the largest ever study in advanced biliary cancer. Based on these findings, the researchers can now establish the first-ever standard of care for these patients.

(Cancer Consultants. com-News, May 20, 2009)

Ginger for Chemotherapy Related Nausea

Despite the use of antiemetics, post-chemotherapy nausea and vomiting are reported in up to 70% of patients. First large multi-site, phase II/III randomized, placebo controlled, double-blind trial conducted at University of Rochester reported that early use of ginger supplements in combination with traditional anti-nausea drugs significantly reduced chemotherapy related nausea in cancer patients. Breast (66%), alimentary (6.5%) & lung (6.1%) cancers were the most common cancer types. Altogether 644 patients were accrued (90% female, mean age 53) and randomly assigned to receive a placebo or 0.5g, 1g or 1.5g of ginger (capsule form) divided into 2 doses given each day for 6 days, starting 3 days before the first day of chemotherapy cycle. All patients also received traditional drugs used to manage nausea associated with chemotherapy. Patients rated their nausea at various times of day during the first 4 days of chemotherapy. All doses of ginger significantly reduced nausea more than placebo, with 0.5 g and 1g doses having the greatest effect.

(www.abstract.asco.org, May 14, 2009)

Sunitinib for Kidney Cancer

Follow-up results of phase III clinical trial of new kidney cancer drug sunitinib (sutent) have confirmed the drug's beneficial effects. Sunitinib is a novel, oral, multi-targeted cancer therapy that selectively targets multiple receptor tyrosine kinase involved in tumor growth, angiogenesis and the progression of cancer. Results show that treatment with sunitinib achieved a median overall survival greater than two years in patients with metastatic cell carcinoma. Sunitinib and interferon-alpha (IFN- α) was 26.4 months vs 21.8 months respectively. Sunitinib has fewer side effects than the injected drug (IFN- α). IFN- α can cause tiredness, nausea and increased susceptibility to infections. These data herald a new era in the treatment of metastatic kidney cancer in UK and throughout the world. With the dawn of such new life extending treatments, researchers are now able to give patients with this difficult-to-treat cancer, more hope for the future.

(J Clinical Oncology, May 18, 2009)

Vandetanib for Lung Cancer

An international phase III trial has shown that the oral targeted therapy vandetanib when combined with standard chemotherapy, improves progression-free survival of patients with advanced non-small cell lung cancer (NSCLC). The therapy is unique in that it's a dual inhibitor and targets the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR). It is the first single agent in lung cancer to target both receptors. As a dual inhibitor, it also may provide cost-savings to patients. The ZODIAC (Zactima in combination with Docetaxel In non-small cell lung cancer) study enrolled 1,391 patients with NSCLC from 198 centers, all had received chemotherapy previously. Participants were randomized to receive either docetaxel and placebo, or docetaxel and vandetanib. The study showed that an oral tyrosine kinase inhibitor can be combined with chemotherapy safely and effectively to provide systematic benefit to patients. The lack of significant side effects is quite striking, because other agents that target VEGF are associated with increased toxicity, including pulmonary bleeding. This study would have immediate clinical implications. Still, it requires focus towards better identifying molecular markers involved, with the ultimate goal of personalizing the patient's care.

(MD Anderson Cancer Center, June 2, 2009)

WATCH-OUT

Breast Cancer Genes Patenting

The BRAC1 and BRAC2 genes are present in every human. However, people with certain genetic mutations on these genes are at an increased risk of developing breast and ovarian cancer. Myriad Genetics, Utah, holds the patent on BRAC1 and BRAC2 with exclusive rights to these genes and their mutations and to the research performed on them. Breast Cancer Action (BCA), a non-profit organization, is challenging the legality of patenting human "breast cancer genes". BCA is also joining the American Civil Liberties Union in suing Myriad. When one company controls all the testing, less information and resources are available to both patients and researchers. Women unable to afford the expensive testing are prevented from access to the test. Moreover, women of African, Hispanic or Asian descent disproportionately receive ambiguous results when tested by Myriad. Injustices and inequities in breast cancer affect genetic risk, as well as social, political and economic realities. Joint litigation would open doors to better research and information, and ultimately better health care for women regardless of their economic situation or their racial background.

(Biocompare News, May 12, 2009)

Prokaryotic Phenylalanine Ammonia-Lyase

Certain cancer cells have a higher metabolic rate and a greater requirement than normal cells for essential amino acids, such as phenylalanine. Restriction or reduction of phenylalanine through the use of enzyme phenylalanine ammonia-lyase (PAL) may reduce growth of certain tumor cells in human cancer patients and in animal models. Prokaryotic or bacterial PAL may serve as an effective treatment for cancer.

United States Patent and Trademark Office has issued patent No 7,537,923 to BioMarin Pharmaceutical Inc. (Novato, CA), entitled "Composition of prokaryotic Phenylalanine ammonia lyase and methods of treating cancer using compositions thereof", published on May 26, 2009. This invention is directed to PAL variants procured by prokaryotes, wherein such prokaryotic PAL variant has a greater phenylalanine-converting activity and/or a reduced immunogenicity as compared to a wild-type PAL. The invention provides compositions of prokaryotic PAL and biologically active fragments,

mutants, variants or analogs thereof and methods for the production, purification, and use of such compositions for the therapeutic purposes, including the treatment of cancer.

(USPTO, June 2, 2009)

Prostate Cancer Metastasis

It has been discovered that the kinase MEK4 regulates prostate cancer cell invasion, a key step in the metastasis of prostate cancer. Univ North Western [US] has been assigned a patent [Publication No. US2009124569 (A1)], entitled "Inhibition and Treatment of Prostate Cancer Metastasis" published on May 14, 2009. The present invention provides compounds and methods of inhibiting and treating metastatic prostate cancer with inhibitors of MEK4 activity. Furthermore, the invention provides methods of screening for inhibitors of metastatic prostate cancer by testing compounds for inhibition of MEK4 activity. Also, compounds for use in methods described herein are disclosed, including anti-MEK4 antibodies, siRNA, genistein and genistein analogs.

(European Patent Office, June 4, 2009)

Stem Cell Targeting of Cancer

Cady Craig and Mcasey Mary of USA have been assigned Patent [publication No. US 2009117050 (A1)] entitled, "Stem Cell Targeting of Cancer, Methods and Compositions Therefor", published on May 7, 2009. The invention discloses methods of detecting and treating a cancer such as an ovarian cancer, using stem cells. Detection methods include administering a plurality of labeled stem cells to a subject having or suspected of having a cancer; and detecting the distribution of the stem cells. In some configurations, the label can be a nanoparticle (like mono-crystalline iron oxide), which can be detected by magnetic resonance imaging.

Treatment methods include administering a plurality of stem cells comprising a therapeutic agent, such as an enzyme which activates a prodrug. In some configurations, the stem cells harbor a nucleic acid sequence encoding a cytosine deaminase, the cells express the enzyme, and the treatment further includes administering the prodrug 5-fluorocytosine, which is converted by the cytosine deaminase to the cytotoxic metabolite, 5-fluorouracil.

(esp@cenet.com, June 2, 2009)

CANCER CONTROL

Breast Cancer Risk Reduction

It is important that women at increased risk of breast cancer be given the option of considering treatments that may reduce their risk. The key recommendations of the newly updated guideline from the American Society of Clinical Oncology are as follows: (i) Pre- and postmenopausal women who have an increased risk of breast cancer may take tamoxifen for five years to reduce their risk of ER-positive invasive breast cancer for up to 10 years. It is not known if there is a benefit of taking tamoxifen for more than five years. (ii) Postmenopausal women at an increased risk of breast cancer may also consider raloxifen for five years to reduce their risk of developing ER-positive invasive breast cancer. Raloxifen may be used for longer than five years in postmenopausal women with osteoporosis in whom breast cancer risk reduction is a secondary benefit. (iii) The use of aromatase inhibitors or retinoids to reduce the risk of breast cancer is not currently recommended outside of a clinical trial. Women taking these drugs would need to consider both the benefits and adverse effects of each agent. In addition, the guideline states that breast cancer risk should be calculated periodically.

(J Clinical Oncology, May 26, 2009)

Chronic Kidney Disease a Cancer Risk

According to a new study, older men who suffer from moderate chronic kidney disease appear to have a higher risk for developing certain kinds of cancer. The study further notes that men with significant kidney disease faced three times the risk for developing cancer, as compared with those who retained normal kidney. So, people with chronic kidney disease need cancer screening and there is a need to pay attention to how these patients are monitored for this risk. It is also important that patients who are referred to organ transplantation, which is one of the best options for people with chronic kidney disease, are carefully worked up regarding immunosuppression, so that people are not transplanted with (hidden) malignancies. The probability of getting both chronic kidney disease or cancer simply goes up with age, so the message here is that even for mild chronic kidney disease, doctors and patients need to be vigilant about being monitored for these concerns.

(HealthDay News, May 2009)

Role of Religion in Cancer Care

Religion often provides a source of comfort and guidance for patients with advanced cancer who are confronting mortality. The results of some studies indicate that individuals who believe in higher power or divine intervention are more likely to want to utilize all measures to extend life. Researchers at the Dana Farber Cancer Institute evaluated religious coping, the act of drawing on faith to cope with the emotional and physical impact of a terminal diagnosis, in order to determine how it impacts the use of intensive, life-prolonging end-of-life care among patients with advanced cancer. Intensive life-prolonging care was defined as the receipt of mechanical ventilation or resuscitation during the final week of life. The results indicated that patients who were identified as "positive religious copers" were nearly three times as likely to receive intensive life-prolonging care when compared with their non-religious counterparts. The results underscore the importance of clear doctor-patient communication in order to meet the individual needs of each patient.

(J American Medical Association, May 8, 2009)

Treatment Option for Hot Flashes

Hot flashes are a major problem in many women and for those who opt not to take hormonal therapies or antidepressants. Gabapentin and a variety of antidepressants are now commonly prescribed for treatment of hot flashes; pregabalin is a newer version of gabapentin. In a phase III double-blinded placebo-controlled randomized trial, three different treatment arms were tested: a placebo versus daily doses of 150 mg of pregabalin (75 mg twice a day) and 300 mg (150 mg twice a day). Researchers found that declines in hot flash frequency were 36 percent for placebo users, 58 percent in women who used lower-dose pregabalin and 61 percent in women given the higher dose. Pregabalin offered about the same benefits as gabapentin. Women who use it only need to take two pills a day, versus three for gabapentin. In the study, side effects were not severe enough that participants stopped using the active study drug any more often than did patients who were taking placebo. Thus, the study offers another treatment option against hot flashes, even in women using anti-estrogen therapies, either an aromatase inhibitor raloxifen or tamoxifen to help prevent the recurrence of estrogen-sensitive breast cancer.

(Mayo Clinic News, May 14, 2009)

GLOBE SCAN

Joint Program on Cancer Control

Latest statistics indicate that cancer will be among the leading causes of deaths, with more than 70% of all cancer deaths occurring in low and middle income countries, where cancer overwhelmingly affects the poor. The International Atomic Energy Agency (IAEA) and the World Health Organization (WHO) have launched a joint program on cancer control, aimed at strengthening and accelerating efforts to fight cancer in the developing world. The joint program will provide the framework to create a more coordinated and robust approach to combating cancer in poor countries. This would mean working with member states to integrate diagnostic and treatment-related activities into cancer control plans of the country based on WHO Cancer Control Guidelines and strategies in each region, which could be far more effective in improving the survival and quality of life of cancer patients. If current knowledge were put into practice, at least one-third of cancer cases could be prevented, another third could be detected early, treated and cured, and suffering could be alleviated through palliative care for patients with advanced cancers.

(Austria: IAEA, May 27, 2009)

Melanoma in Women

During the launch of 2009 SunSmart Campaign, the Irish Cancer Society highlighted that there has been a 36 percent rise in the number of skin cancer cases in Ireland over the past 10 years. This includes a large increase in the number of people diagnosed with melanoma the deadliest form of the disease, particularly among women under the age of 50, who experienced a 75 percent rise in such cases. According to the health protection manager of Ireland, 80 to 85 percent of UV rays pass through clouds and Ireland has the third highest rate of malignant melanoma in the European Union. He advised that one may be out-doors watching sports, doing the gardening or just sitting in the parks, should not let UV rays catch out. If one notices a mole change in shape, colour or size, it should be got checked by a General Practitioner. According to the Irish Cancer Society, 80 to 90 percent of all skin cancers are caused by the sun's UV rays and could therefore be prevented if people take care of their skin.

(Ireland: Cancer Research UK, May 13, 2009)

New Era in Cancer Treatment

An article written by Karol Sikora, Professor of Cancer Medicine at Imperial College, London, highlights an enormous change in cancer medicine with highly personalized treatments, patient top-up payments in some markets, response related payments and even refunds when there is no response to a treatment, all driving the future of cancer care worldwide. Patient knowledge and understanding in terms of what is available has led to the growing use of top-up payments to break access barriers to innovative cancer drugs. An ethically-driven top-up system carries the best chance of sustaining a high-quality care service for all. This is the dawn of a new era of rational cancer drug use, where oncologists avidly seek logical ways to get the right drug to the right patient with personalized diagnostics programs. According to Prof Sikora, within 20 years, cancer would be chronic disease joining conditions such as diabetes, heart disease and asthma. These conditions impact on the way people live and do not inexorably lead to death. The greatest progress would be made in understanding the myriad causes of cancer, leading to new prevention strategies for which scientific advances would be able to provide effective risk reduction.

(UK: Scrip World Pharma News, May 18, 2009)

New Weapon Against Brain Cancer

Scientists have claimed that an 'Electronic Nose' developed by the American Space Agency NASA for air quality monitoring of space shuttle Endeavour can also be used to detect odour differences in normal and cancerous brain cells. Neurosurgeons have used Electronic Nose to investigate the role of cellular odours in cellular trafficking, brain cancer metastasis, stem cell migration and the potential of the device to be used for intraoperative imaging. In a series of experiments, the Brain Mapping Foundation used this device to sniff brain cancer cells and cells in other organs. Their data demonstrates that the device can sense differences in odour from normal versus cancerous cells. This experiment will help pave the way for more sophisticated biochemical analysis and experimentation, and lay the groundwork for further research that may help to better understand cellular trafficking, contribute to designing better approaches for the detection and differentiation of brain cancer and understand the pathophysiology of intracranial gliomas.

(US: Biocompare News, Apr 30, 2009)

IMAGE GUIDED RADIOTHERAPY

Introduction

Image guided radiotherapy (IGRT) is an exciting new area in the field of radiotherapy. Linear Accelerator-Artiste, installed at Rajiv Gandhi Cancer Institute & Research Centre, provides a comprehensive portfolio of image guided and advanced delivery tools enabling to choose the appropriate radiation therapy treatment technique for each patient, make critical adjustments on the spot and deliver Adaptive Radiation Therapy commensurate with the patient's needs.

Enhanced Flexibility

Artiste flexibility gives the ability to create treatment plans that include IGRT, conformal radiation therapy, Intensity-Modulated Radiation Therapy (IMRT), high-precision radiation therapy and also gated treatments. It allows to efficiently and rapidly deliver routine radiation therapy for patients who do not require overly sophisticated plans, while also enabling to deliver more complex treatments using the same platform. Artiste is engineered specifically for Adaptive Radiation Therapy, which aims to precisely deliver dose to the target while sparing surrounding healthy tissues. This is particularly important because the size and shape of tumors change during treatment and because tumors can shift in response to factors such as weight loss, inflammation in nearby tissues, and normal physiological functions. For example, lung tumors move as the patient breathes and the prostate shifts in response to fullness in the bladder and rectum.

To help ensure that the treatment dose is delivered to the target and not healthy tissue, Artiste also offers the ability to incorporate the dose used for pretreatment imaging into the treatment plan so that clinicians can accurately monitor the dose delivered to the patient. Artiste has the ability to choose between multiple imaging options. For patients with simple treatment plans, Artiste offers two-dimensional OPTIVUE™ portal imaging for low-dose, high-resolution image quality. In situations where additional imaging information is required, it offers its powerful and unique 3D MVision™ Megavoltage Cone Beam Imaging. MVision uses the treatment beam to provide 3D target imaging with excellent soft-tissue resolution. MVision also allows clinicians to incorporate dose distributions from cone beam imaging into patient treatment plans.

Rapid Workflow, Improved Outcomes

The images produced are of exceptionally high quality, while maintaining acquisition speed. The speed with which the megavoltage cone beam image is acquired and the speed at which the software arrives at solution for adaptive targeting is three minutes, which is very fast. The system's rapid speed increases patient comfort by decreasing their time on the treatment table and can improve outcomes by minimizing the likelihood that the patient or the target will shift while images are being acquired. Because everything is in line with MVision, so Beam's-Eye-View [BEV] is seen. In-Line™ Technology also streamlines workflow with clear access to the patients. It also increases patient's comfort. Artiste includes the 160™ MLC Multileaf Collimator to provide highly accurate and precise field shaping to the tumor volume, delivering treatment at rapid dose rate of 1000 Mu/minute.

Another feature that increases treatment options for patients is its 550 TxT™ Treatment Table, which accommodates patients of up to 550 pounds (250 kg). The combination of Artiste and Siemens SOMATOM® sensation open large-bore Computed Tomography (CT) system used for planning gives the ability to effectively treat obese patients using the same table for both imaging and treatment, avoiding shifts in patient positioning. Large patients as well as patients with tumors located off-isocenter, also benefit from MVision's extended field-of-view (FOV) option.

Ease of Operation

Patient setup, imaging, verification, and treatment delivery are controlled via Siemens intuitive Syngo® RT Therapist workspace. Adaptive Targeting™ on the software quickly and reliably registers pretreatment images with the planning CT. A streamlined scalable workspace solution provides members of the clinical team with the tools and data they need to efficiently accomplish their tasks.

Conclusion

Flexibility helps ensure that all patients receive the treatment best suited to their needs. Precise treatment delivery maximizes dose to target while minimizing dose to healthy tissue, improving patient outcomes. Rapid image acquisition and treatment delivery enhance workflow and allow clinicians to treat more patients.

(Reviewed by Prof P S Negi, Chief Medical Physicist)



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