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From the Desk of Director Research

The growing population of childhood cancer survivors carries a significant burden of morbidity, necessitating comprehensive long-term follow-up of these survivors with an ultimate improvement in their overall quality of life. "Special Feature" on 'Childhood Cancer Survivors' highlights the major late effects in childhood cancer survivors and the recommended follow-up guidelines. A special thanks to Dr (Mrs) P A Kurkure, Tata Memorial Hospital, Mumbai for providing "Guest Article" on 'Quality of Life in Childhood Cancer Survivors'.

A great challenge in cancer medicine is determining which patient would benefit from a particular cancer therapy. In this era of personalized medicine for cancer patients, gene expression profiling may be helpful in assessing disease prognosis and guiding therapy. The section "Perspective" in this issue portrays 'Gene Expression Profiling: Breast Cancer'.

With the increasing use of mobile phones (i.e, cellular phones and cordless phones), concerns have been raised about its possible carcinogenic effect. "In Focus" gives an overview on 'Mobile Phones & Risk of Tumors'.

Guest lectures by Prof Jame Abraham, West Virginia University, USA; Dr Nick Thatcher, Christie Hospital NHS Trust, UK and Dr Gopal Vijayaraghavan, University of Massachusetts Medical School, USA on 'Breast Cancer', 'Lung Cancer' and 'Adrenal Lesions and Imaging', respectively have been briefly covered under "Activities of RGCI&RC". "Case Reports From RGCI&RC" profile 'Persistent Mullerian Duct Syndrome with Testicular Tumor' and 'Visceral Leishmaniasis Mimicking Abdominal Lymphoma'.

RGCON-2010, an annual International Conference on 'Strategies for Preservation of Organ Structure and Function in Cancer' was organized by the Institute from 25th - 28th March 2010. The conference provided a perfect blend of various clinical specialities. A brief coverage of the conference is reported in this issue.

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

Dr D C Doval

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SPECIAL FEATURE

CHILDHOOD CANCER SURVIVORS

Introduction

Childhood cancer is relatively uncommon with one in 7000 children aged less than 14 years diagnosed in the United States each year[1]. In India, the estimated incidence is about 40,000 per year. Cancer in children has changed over the past 50 years from an inevitably fatal disease to one that is potentially curable. Five-year survival rates of childhood cancers have improved dramatically from 28% in the 1960s to 75% in the 1990s. In the near future one in every 450 individuals in the US population will be a long term survivor of childhood cancer. This has been made possible by advances in supportive care and therapeutic modifications. Contemporary therapy has evolved with the primary aim of not only improving cure but also decreasing the risk of long term sequelae.

Late effects may occur years after completion of therapy and this raises important issues regarding how frequently they should be monitored and what kind of follow up should be offered. The frequency of monitoring should be sufficient to detect late effects as early as possible without causing unnecessary distress to the survivors.

The wide range of late effects requires a multidisciplinary approach and the increasing number of survivors puts stress on the limited resources available and also raises the issue that they maybe too old to attend children's services[2]. Most of these children are being followed up by a primary care physician who may not be well versed with all the aspects of long term sequelae. The patients also need to be aware of the long term risks so that they maintain meticulous records of the type of cancer and the therapy given to them. By documenting and anticipating these sequelae a regimen can be formulated to reduce the frequency and severity of morbidity in children.

Late Effects

Approximately two-thirds of the survivors experience physical or psychosocial late effects[3]. These effects may occur within 5 years to more than 20 years from completion of treatment[4]. The commonly seen physical late effects include endocrine dysfunction, cardiomyopathy, second malignancies and gonadal dysfunction. Apart from these physical disabilities, cancer survivors can have learning problems, difficulty in making friends and establishing intimate relationships. They also have a constant fear of relapse, uncertainity about future health, limitations due to late effects and compromised physical and social functioning.

Discussed below are the major late effects and the recommended follow up guidelines.

Neurocognitive Sequelae

The potential for neurocognitive dysfunction is probably the most worrisome outcome for the survivors and parents. It occurs as a consequence of cranial radiation, high dose methotrexate, cytarabine therapy and intrathecal methotrexate. Neurocognitive dysfunction is commonly seen in survivors of central nervous system (CNS) tumors, acute lymphoblastic leukemia and to some extent also in patients treated with a stem cell transplant or with radiation to head and neck tumors.

Most of the children present with loss of acquisition of new skills at a rate similar to their peers rather than loss of existing skills and knowledge[3]. They usually present to the primary care physicians with school difficulties and problems related to attention and concentration, processing speed, visual perceptual skills, receptive and expressive language and memory[5]. Most of these children have history of committing careless errors, incomplete assignments and inconsistent academic performance. Mathematics, reading and spelling are the frequently impacted areas. Simple methods, such as seating the child in the front row of the classroom, reducing the number of items or multiple choice tests, breaking assignments and allowing more time to complete assignments often help in improving school performance[5].

Screening Guidelines: Baseline neuropsychological assessment of all survivors who are at risk of neurocognitive side effects is recommended. A repeat assessment at key transition points should be done and also when clinically indicated.

Psychosocial Issues

The experience of being diagnosed with cancer puts considerable pyschologic strain on patient and the family. It was seen that on an average cancer survivors are more likely to present with mental health disorders with 17% of young adult survivors reporting depressive, somatic or anxiety symptoms[6]. However, the survivors

are less likely to exhibit risky behaviors like cigarette smoking or drug use. Hence, physicians should be sensitive to the concerns of the survivors regarding school completion, job opportunities and issues associated with fertility and parenthood.

Growth

Severe growth retardation (height < 5th percentile) is seen in one-third of the survivor children with brain tumor and in 10-15% of children on antileukemia regimens[3]. The younger children who receive cranial irradiation are at maximum risk. The primary cause is hypothalamic damage with impaired secretion of growth factor releasing hormone. Radiotherapy related injury to musculoskeletal tissues is generally more common in younger age children.

Screening Guidelines: Monitoring height using standard growth charts is recommended and endocrine consult is taken if height < 3rd percentile, crosses 2 percentiles or growth rate is < 4-5 cm/yr.

Cardiovascular Function

Cardiotoxicity usually manifests as cardiomyopathy, pericarditis and congestive cardiac failure. Anthracycline induced cardiomyopathy is a well known entity. A cumulative dose of 250 mg/m^2 along with radiation to heart is associated with a higher risk of heart failure (CI 20% at 25 years) as compared with a cumulative dose of <250 mg/m^2 (CI of 5%)[7]. The incidence of asymptomatic cardiotoxicity ranges from 0-56% in various studies. The risk factors for anthracycline cardiotoxicity include higher cumulative dose, radiotherapy involving the heart and in some studies younger age and female sex.

Coronary artery disease has been reported after mediastinal radiation with a cumulative risk of 21% at 20 years[8]. The cumulative incidence of myocardial infarction after mediastinal irradiation is 12.9%[8]. Acute lymphoblastic leukemia survivors are more likely to be physically inactive, have increased visceral adiposity, develop insulin resistance and dyslipidemia at a young age and are hence at a higher risk to develop coronary artery disease. It is mainly related to cranial radiation but also seen in children who receive chemotherapy alone.

Chronic cardiotoxicity with radiation alone usually presents as pericardial effusions and constrictive pericarditis usually with doses exceeding 40Gy[3]. Restrictive cardiomyopathy with diastolic function is seen in patients who receive radiation alone, and systolic dysfunction is seen predominantly in those who receive anthracyclines also.

Screening Guidelines: Yearly history and clinical examination with a baseline ECG is recommended. Periodic echocardiogram is to be done based on dose and age at exposure. A fasting sugar and lipid profile yearly is also to be done.

Gonadal Toxicity

Male Gonadal Function: The germinal epithelium of the testis is sensitive to radiation which results in a loss of testicular volume and sperm production and increased follicle-stimulating hormone (FSH). Effects are dose dependent with exposures ranging from 0.1 to 6 Gy. Patients treated with 3-4 Gy can recover spermatogenesis[3]. Radiation therapy is less toxic to Leydig cells and damage occurs at higher doses and leads to delayed sexual development with decreased testosterone levels and increased luteinizing hormone (LH) levels. Radiation to the hypothalamic-pituitary axis may result in gonadotropin deficiency and affect spermatogenesis.

Spermatogenesis is also quite affected by several chemotherapeutic agents (alkylating agents, procarbazine and cisplatin). Outcomes are agent specific and dose dependent. Treatment with moderate to high dose cyclophosphamide or ifosfamide as in Ewing sarcoma patients causes infertility in virtually all males. Similarly use of cisplatin with alkylating agents in osteosarcoma results in oligozoospermia or azoospermia in over 90% males[9]. Gonadal damage after cumulative dose of cyclophosphamide < 7.5 g/m^2 is reversible in upto 70% patients. Sperm cryopreservation is an effective method of fertility preservation.

Female Gonadal Function: Ovaries during childhood are relatively resistant to chemotherapy induced damage but are sensitive to radiation. Among the 3,390 survivors in the childhood cancer survivor study, acute ovarian failure was reported in 6.3%. More than 70% women who received 2000 cGy radiation to ovary had acute ovarian failure[6]. The risk of acute ovarian failure was increased if the women also received alkylating agents along with radiation. Females who are more than 10 years and receive total body irradiation also have a very high risk of developing acute ovarian failure. Apart from acute ovarian failure, they are also at a risk of developing premature menopause. The consequences of acute ovarian failure and premature menopause also lead to alteration in bone metabolism leading to osteoporosis and sexual dysfunction.

Screening Guidelines: Evaluation includes a detailed history with Tanner staging of breast and genital

development. Serum FSH, LH and estradiol levels should be obtained as a baseline at 13 years and as clinically indicated.

Second Cancers

It has been clearly demonstrated that childhood cancer survivors are at a six-fold increased risk to develop a second cancer as compared to the general population[3]. The risk depends on host factors (genetics, immune function, hormonal status); primary cancer therapy; environmental exposure and lifestyle factors. The standardized incidence ratio of developing second malignancies in the childhood cancer survivor study cohort was 6.38(5.69-7.31 95%CI)[10] and 7.92 for developing secondary acute myeloid leukemia (AML).

The common second cancers include solid tumors and therapy related myelodysplastic syndrome and AML. Ionizing radiation is associated with several solid tumors depending on the dose of radiation and increasing age of the child. The common solid tumors include the breast, thyroid, CNS, bone and soft tissue. Breast cancer is the commonest secondary solid tumor with incidence rates ranging from 10-20% by 20 years from radiation. Female patients treated with mantle field radiation for Hodgkin lymphoma before 30 years of age are at high risk to develop breast cancer. Secondary AML develops with exposure to alkylating agents and topoisomerase II inhibitors. It usually develops 5 to 10 years after alkylating agent use and within 2 to 3 years of use of topoisomerase II inhibitors. The risk of alkylating agent induced leukemia is related to cumulative dose, whereas the risk of topoisomerase II inhibitor related leukemia is both dose and schedule related.

Screening Guidelines: Recommendations include yearly complete blood count monitoring and meticulous physical examination for 10 years after exposure to alkylating agents or topoisomerase II inhibitors. In case the patient has received radiation impacting thyroid a yearly thyroid examination is indicated. Patients who are at high risk of developing breast cancer should carry out monthly self-breast examination and yearly clinical breast examination till 25 years of age and then every 6 monthly. Mammogram with MRI is to be done yearly beginning 8 years after radiation or at age 25 whichever is later.

Future: Risk Based and Shared Care Model

As the risk and severity of several late effects is preventable long term follow up of childhood cancer survivors is recommended. A systematic plan for longitudinal screening, surveillance and prevention that incorporates risk based on previous cancer, cancer therapy and genetic predisposition is recommended.

In view of limited resources available for long term follow up a shared care model should be formulated which involves participation of the primary care physician along with the oncologist.

Conclusion

Extensive research has linked therapeutic exposure with specific treatment complications. Proactive and anticipatory risk based care can reduce the frequency and severity of treatment related morbidity. Health screening guideline resources can be used to facilitate survivor care. Coordination of an individualized shared care plan between oncologists and primary care physicians is essential to optimize long term risk based survivor care.

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GUEST ARTICLE

QUALITY OF LIFE ISSUES IN CHILDHOOD CANCER SURVIVORS

Introduction

Improvements in cancer therapy over the last several decades have made it possible for more children surviving cancer than ever before, resulting in a growing population of childhood cancer survivors, an estimated 270,000 survivors in US alone. This burgeoning population creates an obligation to focus on long term complications of cancer treatment and health related quality of life (HRQOL) of survivors. One of the major goals of healthcare systems is to help cancer survivors maintain highest possible quality of life.[1]

Quality of Life (QOL) is a broad concept that includes physical, psychosocial, emotional, and spiritual components.

Physical Component

Known physical late effects are:

- Neurocognitive deficits in those receiving cranial RT/ IT Mtx/high dose Mtx/ARA-C.
- Cardiac problems such as cardiomyopathy, early onset atherosclerosis who have received chest RT and/ or anthracyclines.
- Pulmonary problems like pulmonary fibrosis, restrictive/ obstructive lung disease, particularly in bleomycin exposure, RT to lungs.
- Endocrine system-hypothyroidism is common following RT to neck. Other endocrine problems include growth hormone deficiency, hyperprolactenemia.
- Infertility in survivors treated with alkylating agents, surgery/RT to gonads.
- Second malignancy. Follow up of large cohort of childhood cancer survivors demonstrated a six-fold higher risk of developing a second cancer as compared to general population and this risk continues to increase as cohort ages.[2]

Review of literature suggests that the risk of having a limited physical performance is increased with tumors located in bone, brain or mediastinum and with radiation to head, brain or chest. Survivors treated with alkylating agents or anthracyclines or combinations of two, are at increased risk. The chemotherapy and radiation group is more likely than surgery-only group to report physical performance limitation. Female sex and low socio-economic status are also associated with poorer outcome.[3]

Psychosocial & Emotional Component

Although majority of childhood cancer survivors are psychologically well adjusted,[4] certain groups of survivors are at a high risk for adverse psychological outcome, with poor QOL.

The high risk factors include:

- Female sex
- Lower educational attainment
- Unmarried status
- Unemployment
- Lack of health insurance
- Presence of major late effect
- Treatment with cranial RT and/or surgery.

Results from **C**hildhood **C**ancer **S**urvivor **S**tudy (**CCSS**) clearly identified brain tumor survivors as a particularly vulnerable group. This high risk group reports more psychological distress, fatigue, cognitive problems and diminished life satisfaction.[5]

Similarly, survivors are at risk of undesirable social outcomes in areas such as education and career, friendships and social interactions, employment and financial independence, intimate relationships and marriage. Brain tumor survivors seem to be at a particularly higher risk.[6]

These sequelae are not only related to the specific therapy employed but are also determined by individual host characteristics. Also culture plays an important role. Culture and geographical location affect their access to the follow up clinic. Despite their individual culture differences, many cancer survivors share common traits, experiences and concerns.

Spiritual Component

To win the battle against cancer, one requires strength, resilience, patience and flexibility. Surviving cancer is like a spiritual journey that teaches how to change your life. In course of coping with cancer, survivors can learn to respect their own emotions and to distinguish them from irrational and unhelpful worries contributing to poor quality of life.

Assessment of QOL

With reference to WHO definition of health , quality of life can be defined as a multidimensional construct, that

incorporates both objective and subjective aspects, including the social, physical, and emotional functioning of the child and, when indicated, his/her family.

There are questionnaires/instruments to assess quality of life, such as the Minneapolis-Manchester Quality of Life (MMQL) instrument[7] to address the critical need for a practical and comprehensive, multidimensional, self-report assessment of QOL in survivors of childhood cancer.

Three versions of the MMQL address the changing developmental need of different ages:

- MMQL-Youth Form (8 to 12 years; interview-based)
- MMQL-Adolescent Form (13 to 20 years; self-administered)
- MMQL-Young Adult Form (21 to 45 years; self-administered).

Other methods of assessment include Brief Symptom Inventory (BSI-18), the Medical Outcomes Survey Short Form-36 (SF-36), the Cantril Ladder of Life, and other self-report questionnaires.[5]

These instruments are not validated in the Indian context and hence there is limitation in their application.

It is essential to be aware of **"at-risk"** population amongst the survivors. Children's Oncology Group has developed a risk-based, exposure related guide to assist institutions in establishing and enhancing long term follow up programmes and services for childhood cancer survivors.[8] This can be used as a template on which institutes can formulate their own guidelines.

Drawing inspiration from the model of care established at St Jude Children's Research Hospital, USA, follow-up clinic for long term survivors of childhood cancer was initiated at Tata Memorial Hospital in February 1991. This clinic was appropriately named **A**fter **C**ompletion of **T**herapy (**ACT**) Clinic to emphasize that **ACTs** are needed beyond therapy to achieve **CURE²** in its full dimensions. This clinic aims to monitor growth, development, sexual maturation and somatic late effects of therapy and to apply corrective measures whenever feasible.[9] Survivors are also evaluated for psychosocial aspects. The severity of late effects is graded according to Garre's Grading System.[10]

Over eleven hundred childhood cancer survivors have been registered in the ACT Clinic from February 1991 to February 2010. Overall 46% (511) exhibited no evidence of cancer related complications (Grade 0); 20% (218) survivors had asymptomatic laboratory changes detected by health screening (Grade 1, e.g. incidentally detected asymptomatic HBsAg status); 9% (105) had moderate symptomatic changes that could be corrected by simple therapeutic interventions (Grade 2, e.g. thyroid hormone replacement therapy) 20 % (216) had severe impairment, such as cosmetic changes, reproductive dysfunction and learning deficits requiring special support (Grade 3); 5% (59) experienced life threatening events, such as late primary cancer recurrence, development of second malignancy or death (Grade 4).

Although not measured objectively, survivors with Grade 3 and Grade 4 late effects have clearly evident poor quality of life due to physical component. Survivors with Grade 1 and Grade 2 late effects are also vulnerable due to chronic stress of uncertain health outcome (e.g. incidentally detected asymptomatic HBsAg positive survivors).

Many survivors want to share their experiences and knowledge with others like them. They want to give back to their communities, help community members with their cancer experiences, and dispel myths that cancer is not a death sentence. Learning from their own experiences, survivors can give back by teaching healthcare teams how to provide culturally sensitive care, participating in peer support and advocating on behalf of survivors with whom they share a common culture. Such team efforts not only improve QOL of survivors but also of cancer patients with whom they interact.

Childhood cancer survivors from ACT Clinic of Tata Memorial Hospital, inspired by such team efforts of survivors from across the globe with whom they interacted during International Society of Pediatric Oncology Meeting in October 2007, came together on 7th June 2009, first Sunday in June, celebrated it as Cancer Survivors Day. They formed a voluntary support group, which they christened as **UGAM**, which means **"To Rise",** underscoring their determination to rise above all obstacles in life and be **VICTORS.** UGAM is the youngest unit of the oldest and most prominent NGO, The Indian Cancer Society (www.indiancancersociety.org), under its survivorship program.

Its vision is:

- To ensure that every childhood cancer survivor finds his/her way to celebrate life after winning battle with cancer.
- To facilitate their life's journey on correct path and in right direction.

UGAM provides a helping hand to the survivors of childhood cancers and to become an ambassador of the message **"Childhood Cancer is Curable"** in society.

Conclusion

Identification of childhood cancer survivors at risk for poor quality of life is important for early intervention.

Long term follow up clinic for childhood cancer survivors provides a platform where complete assessment of survivors can be done and services can be provided to improve their quality of life.

Peer support can have a profound impact on how the survivors feel about themselves and how well they manage their lives during and after cancer.

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PREFERRED RESEARCH CENTRE

Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC) is a comprehensive cancer care set-up with all the facilities for diagnosis and treatment for all types of cancer. The hospital has several accreditations and achievements to its credit for quality and excellence. RGCI&RC also conducts training programs in clinical research in partnership with Indian and foreign collaborators.

To promote education and research, especially clinical research in the field of oncolgy, RGCI&RC has recently collaborated with Pfizer Limited, which is public limited pharmaceutical company engaged in clinical research since past fifteen years in India. Pfizer would provide RGCI&RC an educational grant over a period of five years as per terms of the agreement. RGCI&RC would utilize this grant to set up a **Preferred Research Centre** with the purpose of achieving following objectives:

- To develop knowledge and skills in clinical research by conducting training programs in regulations, ethics, clinical trial methodology, clinical trial management and statistics, protocol writing, good clinical practice for clinicians and clinical research coordination etc.
- To develop clinical research secretariat in RGCI&RC as a central nodal site for all clinical trials activities in the Institute.
- To develop RGCI&RC as a referral centre for other smaller clinical research sites in the surrounding areas of the Institute.

The terms of the agreement will not preclude RGCI&RC from undertaking clinical research activities in collaboration with other pharmaceutical companies, organizations or by self.

PERSPECTIVE

GENE EXPRESSION PROFILING: BREAST CANCER

Introduction

Gene expression profiling is an emerging technology for identifying genes whose activity may be helpful in assessing disease prognosis and guiding therapy. It has been widely applied to cancer research in the past few years and the recent development of microarray and related technologies have provided an opportunity to perform more detailed and individualized tumor characterization.

In the current clinical practice, the majority of patients with early breast cancer receive some form of systemic adjuvant therapy (chemo- and/or endocrine therapy). Patients with similar clinicalopathological features may show distinct outcomes and vary in their response to therapy. Even though algorithms based on clinicopathological data are now regularly used to define prognostically significant groups and to tailor systemic therapy for breast cancer patients, additional prognostic factors are required to improve patients' risk stratification and targeting of treatment, so as to "personalize medicine". Expression profiling and other technologies have helped in discovering relevant signatures potentially related to prognosis (clinical outcome), prediction (tumor response to a specific therapy), and providing further insights into tumor biology.

Methods

Molecular profiling of breast cancers by gene expression microarrays can be performed in two ways: unsupervised or supervised analysis. Unsupervised analysis is a statistical method and the main objective of this approach is to determine whether discrete subsets can be defined on the basis of gene expression profiles and to identify new classes (class discovery) potentially having clinical significance in order to develop a new molecular taxonomy. In supervised analysis, external information is used to group the samples (tumor grade, gender, response to therapy) or the genes (functional class, chromosomal location) and relate the grouping with gene expression data.

Molecular Classsifcation

Breast cancers can be classified into five distinct molecular subtypes based on their microarray expression: two ER positive subtypes (luminal A, luminal B), basal subtype, HER2 positive and normal breast like subtype. In general, luminal A tumors have the highest expression of ER and ER related genes, and show the best prognosis. Luminal B tumors show low to moderate expression of ER related genes, relatively high expression of proliferation and cell cycle-related genes and are associated with less favorable outcome.

Basal-like, ERBB2/HER2/neu/+, and normal breast-like tumors are hormone receptor negative breast cancers but are otherwise molecularly and biologically different. Basal-like cancers express genes characteristic of basal myoepithelial cells *(CK5, CK17, c-KIT, EGFR laminin, metallothionein 1X, NF-kappaB, and P-cadherin)*. Basal-like tumors usually have aggressive features such as high tumor grade and *TP53* mutations and poor outcome. Patients carrying *BRCA1* mutations fall within the basal-like subgroup. ERBB2/HER2/neu/+ tumors are characterized by overexpression of genes in a 17q11 amplicon that include *ERBB2*, *GRB7*, *GATA4,* and high levels of *NF-kappaB* activation. Like the basal-like subtype, *ERBB2* - overexpressing tumors have a high proportion of *TP53* mutations, and are significantly more likely to be grade III and compared with basal-like group, share comparatively poor outcomes. Normal breast-like tumors share characteristics with normal breast tissue like relative overexpression of basal epithelial genes and relative under-expression of luminal epithelial genes. Invasive lobular breast cancers often show normal breast like expression profiles and show better prognosis than that of basal-like cancers and do not appear to respond to neoadjuvant chemotherapy at the same rates as other tumors pertaining to the ER-cluster.

Prognostic Markers

Several independent groups have conducted comprehensive gene expression profiling studies with the aim of improving upon traditional prognostic markers used in the clinic. The **MammaPrint™ assay** is the first fully commercialized microarray-based multigene assay, using fresh unfixed tumor tissue, designed to individualize treatment for patients with breast cancer. The 70 genes that comprise the MammaPrint assay are focused primarily on proliferation with additional genes associated with invasion, metastasis, stromal integrity and angiogenesis. It is offered as a prognostic test for women under the age of 61 years with either ER positive or negative, lymph node-negative breast cancer. This assay was validated by the Translational Breast International Group

(TRANSBIG) research consortium. Recently, a pooled analysis of 1,637 patients across Europe reported that the 70-gene MammaPrint profile is not only a strong and independent prognostic indicator for patients with early stage breast cancer, but it may also be predictive for the benefit of chemotherapy. While MammaPrint "high risk" classified patients demonstrate a clear benefit, those of "low risk" do not appear to benefit from the addition of chemotherapy to hormonal treatment alone.

21-gene Oncotype DX ™ assay, developed commercially, quantifies gene expression for 21 genes in breast cancer tissue (see Table) by real-time reverse transcription polymerase chain reaction (RT-PCR), using formalin-fixed, paraffin-embedded tumor tissues. This test is intended to predict the likelihood of recurrence in women of all ages with newly diagnosed Stage I or II breast cancer, lymph node-negative and ER-positive, who will be treated with tamoxifen, an anti-estrogen agent. National Surgical Adjuvant Breast and Bowel Project B-20 trial concluded that this assay not only quantifies the likelihood of breast cancer recurrence in women with node-negative, estrogen receptor-positive breast cancer, but also predicts the magnitude of chemotherapy benefit. Oncotype DX is furthest along the validation pathway, with strong retrospective evidence that it predicts distant spread and chemotherapy benefit. In the United States, Oncotype DX is currently the most commonly used assay in clinical practice. Limitation to the use of this assay is lack of a data driven answer regarding the optimal treatment of patients with an intermediate-risk recurrence score (RS). It is limited to patients with ER-positive disease, unlike other assays (including the MammaPrint assay).

A **diagnostic test (VDX2)** is also being developed by Veridex, using a set of 76 genes (the Rotterdam gene set) that were identified in a study of gene expression profiles of 286 lymph node-negative patients who had not received adjuvant systemic treatment. This signature was able to predict distant metastatic recurrence with a sensitivity of 93% & a specificity of 48%. This prognostic indicator performed better than standard, clinical variables in a multivariate analysis. **Mammostrat®** is a five-antibody panel, which distinguishes tumors with a high risk versus low risk for recurrence. It was validated in two cohorts of patients, with the Cox model distinguishing ER-positive patients with poor outcomes from patients with good or moderate outcomes, but this model was not useful for ER negative patients. Clinical utility of Mammostrat® panel may be in postmenopausal patients. A successful predictor of local recurrence identified is the wound-healing or **wound response indicator (WRI) signature**, which correctly predicted local recurrences with a sensitivity of 88% and specificity of 74%. Number of local recurrences in the dataset was low (17/161), and these results need to be confirmed in a larger study.

MammaPrint® test, WRI, and Oncotype DX ™ assay have been compared using a single dataset of breast cancer samples from 295 women. The indicators showed high rates of concordance in predicted outcome for individual patients, regardless of the minimal gene overlap among the assays, suggesting that the concordance of the predictors is a result of common cellular phenotypes, detected by the various predictors. Even though there was discordance among the involved genes, these indicators detected common sets of biological characteristics determining patient outcomes.

Predictive Markers

In clinical practice, chemotherapy is applied empirically despite the fact that not all patients benefit from those agents. Hence, there is an imperative need to identify predictive biomarkers for its efficacy. Studies suggest that benefit of estrogen therapy is proportional to the level of ER expression; therefore, quantitative ER measurements assays are important. ER status is determined by performing immunohistochemistry on formalin-fixed, paraffin-embedded tumor tissue, but

TABLE: PANEL OF 21 GENES

Proliferation Genes	Invasion Genes	HER 2	Estrogen	Other Cancer-Related Genes	Reference Genes
Ki-67, STK 15, Survivin, CCNB1 (cyclin B1), MYBL 2	MMP11 (stromolysin 3), CTSL2 (cathepsin L2)	GRB7, HER2	ER, PR, BCL2, SCUBE2	GSTM1, CD68, BAG 1	ACTβ (β-actin), GAPDH, RPLPO, GUS, TFRC

MYBL2 indicates v-myb myeloblastosis viral oncogene homolog (avian)-like 2; MMP11, matrix metalloproteinase 11; GRB7, growth factor receptor-bound protein 7; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; GSTM1, glutathione S-transferase Mu 1; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; RPLPO, ribosomal large protein; TFRC, transferrin receptor (p90, CD71).

these assays have considerable variation in tissue fixation, antigen retrieval, staining techniques, and interpretation of results across laboratories. Today, the expression of the ER is measured at the mRNA level using RT-PCR or microarrays, which are more quantitative than immunohistochemistry.

Several small studies have provided "proof-of-principle" that the gene expression profile of cancers highly sensitive to chemotherapy is different from the gene expression profile of tumors that are resistant to treatment. Taxanes are a class of antimicrotubule agents that are routinely used in multidrug therapy of breast cancer. A **92-gene panel** was developed as potential predictor of response to taxanes. Tumors from patients with primary breast cancer were biopsied prior to neoadjuvant treatment with docetaxel. Gene expression patterns were then correlated with a response to docetaxel. In cross-validation experiments, docetaxel-sensitive and docetaxel-resistant tumors with 92% specificity and 83% sensitivity were detected. More studies are needed to further validate this predictor. It was recently demonstrated that patients with advanced breast cancer also showed that topoisomerase *TOP2A* overexpression was associated with a higher probability of response to single-agent doxorubicin but not to single-agent docetaxel. Recently, FDA approved a ***TOP2A* fluorescence in situ hybridization assay** to measure amplification of this gene in breast cancer specimens.

A comparison of ER-positive tumors obtained from tamoxifen responders and non-responders with advanced breast cancer led to the identification of **44 genes** that are differentially expressed in these tissues. The predictive power of this signature was considerably superior to that of traditional predictive factors in a univariate analysis and it was associated with a longer progression-free survival time in univariate and multivariate analyses. It was also demonstrated that a **two-gene ratio** (***HOXB13/IL17BR***) was predictive of disease-free survival in patients with early-stage, ER-positive breast cancer who received treatment with tamoxifen. An RT-PCR based method to assess this ratio from paraffin-embedded tissue samples is now commercially available.

Future Directions

Despite these advances, there are multiple unresolved issues: there are very few data regarding the biologic reproducibility of these assays; the effect of variable tumor cellularity as well as intratumoral heterogeneity on the molecular classification; and the potential for contamination by normal breast tissue or in situ carcinomas, particularly in small invasive tumors. Furthermore, the usefulness of these assays in other clinical settings (eg, in patients with locally advanced or metastatic breast cancer) has not been adequately examined. Currently a prospective randomized clinical trial, TAILORx [Trial Assigning IndividuaLized Options for Treatment (Rx)]: is assessing the value of adjuvant chemotherapy among patients with mid-range RS results. MINDACT (Microarray for Node-Negative Disease may Avoid Chemotherapy), a multi-centre, prospective study is comparing use of the MammaPrint assay with a common clinical-pathological prognostic tool, to select patients for adjuvant chemotherapy in node-negative breast cancer. These trials, along with the incorporation of tissue collection and genomic profiling into general clinical trial design, will improve the ability to optimally tailor therapy for individual patients.

Conclusion

The introduction of these gene-expression tests has ushered in a new era in which many conventional clinical markers and predictors may be seen merely as surrogates for more fundamental genetic and physiologic processes. The multidimensional nature of these predictors demands large numbers of clinically homogeneous patients to be used in the validation process. Every study provides an opportunity to tweak a genetic signature, but the right balance must be found between speed of innovation and development of scientifically and clinically reliable tools. Going forward, it will be important to harness, if possible, as much genetic and clinical information on patients who undergo these tests to facilitate each goal without unduly sacrificing the other.

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(Reviewed by Dr Suresh P, DNB student; Dr DC Doval, Chief, Dept of Medical Oncology & Director Research)

MOBILE PHONES & RISK OF TUMORS

Modern lifestyle is leading to a fast change in our daily life and at majority of occasions we are left with no option except to adapt ourselves to the technological advancements such as mobile phones. With the increasing use of mobile phones (i.e, cellular phones and cordless phones), concerns have been raised about its possible carcinogenic effects because of the exposure to radiofrequency EMFs (Electromagnetic fields) ranging from 800 to 2000 MHz, which fall in the microwave spectrum. Over the past decade, case control studies also have reported the relationship between the use of mobile phones and malignant or benign tumors, such as brain tumors, head and neck tumors, non-Hodgkin's lymphoma and testicular cancer. Some other case control studies have reported no significant association.

The report, "Cellphones and Brain Tumors: 15 Reasons for Concern, Science, Spin and the Truth Behind Interphone" released by International Electromagnetic Field Collaborative on Aug 26, 2009, provides information on scientific findings of various studies on the risk of brain tumors from cellphone use. Studies, independent of industry, consistently show there is a significant risk of brain tumors from cellphone use. The design flaws in the Interphone study protocol resulted in an underestimation of the risk of brain tumors from cellphone use. The electromagnetic field exposure limits advocated by industry and used by government are based on a false premise that a cellphone's electromagnetic radiation has no biological effects except for heating.

Meta-analysis of mobile phone use and intracranial tumors by Lahkola et al. concluded that evidence does not indicate a substantially increased risk of intracranial tumors from mobile phone-use for a period of at least 5 years. Meta-analysis by Peter Kan et al found no overall increased risk of brain tumors among cellular phone users. While the meta-analysis by Hardell et al. gave a consistent pattern on an association between mobile phone use and ipsilateral glioma and acoustic neuroma using ≥ 10 years latency period. Meta-analysis of case control studies of Myung et al found evidence linking mobile phone-use to an increased risk of tumors.

In the meta-analysis of 23 case control studies, Myung et al identified a total of 37,916 participants (12, 344 patient cases and 25, 572 controls) having a mean age of 52.6 years. In a random-effect meta-analysis of all 23 studies, the odd ratio (OR) for overall use was 0.98 for malignant and benign tumors compared with never or rare use of a mobile phone. A significant positive association (harmful effect) with OR of 1.17 was observed in random effects meta-analysis of eight studies using blinding. A significant negative association (protective effect) with OR of 0.85 was observed in a fixed-effects meta-analysis of 15 studies not using blinding. Meta- analysis by methodologic quality of study revealed a significant positive association in the high-quality studies with OR of 1.09, whereas negative association was observed in the low quality studies. Mobile phone-use of 10 years or longer was associated with a risk of tumors in 13 studies with OR of 1.18. Unlike the previous meta-analysis while performing subgroup analysis, the researchers found significant association between mobile phone-use and risk of tumors in low-biased, case control studies, which were mostly studies by Hardell et al.

The risk of brain tumors from cellphone-use is highest in children. In addition, cellphone radiation has a negative impact on male fertility (sperm count and motility). Cellphone user manual warns customers to keep the cellphone away from the body (e.g., held to the ear, in a shirt pocket, in a pants/trousers pocket etc.) even when the cellphone is not in use. Use of cellphone in a moving vehicle, or in rural areas at some distance from cell tower should be avoided as it increases power of cellphone's radiation. Children should not be allowed to sleep with a cellphone beneath their pillow or at the bed side.

Some government recommendations and guidelines have been published in this regard, but no mandatory actions have been taken so far. Prospective cohort studies should be undertaken in this area to provide a high level of evidence.

Suggested Readings

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3. Kan P, Simonsen SE, Lyon JL, et al. Cellular phone-use and brain tumor - Meta-analysis. *Neurooncol* 2008; 86: 71-78.

(Reviewed by Dr Sajjan Singh, DNB student; Dr Sunil Kr Gupta, Sr Consultant, Dept of Medical Oncology)

ACTIVITIES OF RGCI&RC

BREAST CANCER

Prof Jame Abraham, Chief Section of Hematology-Oncology, Medical Director, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV, visited Rajiv Gandhi Cancer Institute and Research Centre (RGCI& RC) on February 18, 2010 and delivered a guest lecture on "Evolving role of biological agents in the treatment of breast cancer". The lecture was attended by Dr DC Doval, Director Research, Consultants, DNB students and Research Officers of the Institute.

Breast cancer is the most commonly diagnosed malignancy in women and is the second leading cause of cancer death. Recent microarray expression profiling analysis has characterized breast cancer into five main subgroups; luminal A, luminal B, normal breast like, human epidermal growth factor receptor 2 (HER 2) and basal-like. Systemic treatment of breast cancer is constantly evolving as more active chemotherapeutic agents are becoming available and biological factors have been incorporated into decisions on treatment .

Trastuzumab (Herceptin), a humanized monoclonal antibody, selectively targets HER 2, which is over-expressed in 15-25% of breast tumors and its over-expression is associated with increased disease recurrence and poor prognosis. Trastuzumab has been shown to provide significant clinical benefits to patients with HER2-positive breast cancer when given alone or in combination with chemotherapy.

Prof Abraham mentioned about treatment trials regarding breast cancer patients with over-expression or amplification of the *HER2/neu* gene. BCIRG 006 study showed that HER 2 positive cancer patients, regardless of its hormone receptor status, may be served well by a non-anthracycline regimen, such as Taxotere/ Carboplatin/Herceptin (TCH). The study indicated that non-anthracycline regimen containg trastuzumab is a viable option in the treatment of HER-2+ve patients with breast cancer. The US Food and Drug Administration (FDA) has approved TCH for the adjuvant (post-surgery) treatment of HER2 positive early breast cancer.

Bevacizumab, a humanized monoclonal antibody, targets vascular endothelial growth factor to reduce tumor angiogenesis. National Surgical Adjuvant Breast and Bowel Project (NSABP) B-46-1, a Phase III trial for breast cancer patients (node-positive or high-risk node-negative) but HER2-Negative is being evaluated to see that adding bevacizumab to standard chemotherapy treatment (docetaxel, doxorubicin & cyclophosphamide) would prevent breast cancer from recurrence and provide longer life to the patient The final results of trial are awaited. Another trial of Eastern Cooperative Oncology Group (ECOG) 5103, a randomized Phase III trial for breast cancer patients with high risk of recurrence is evaluating the potential benefit of adding bevacizumab to standard chemotherapy. BETH study for the treatment of HER2 positive breast cancer patients with resected node-positive or high risk node-negative is comparing chemotherapy plus trastuzumab with chemotherapy plus trastuzumab and bevacizumab to determine the value of adding bevacizumab to chemotherapy plus trastuzumab.

Lapatinib, a dual tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR) and HER2, has shown clinical benefit in trastuzumab refractory breast cancer and is approved by the US FDA. Prof Abraham mentioned about the adjuvant lapatinib and/or trastuzumab treatment optimisation (ALTTO) study, to find out whether one drug will prove better than the other at helping women live longer without a recurrence of their disease, or if the two drugs will work better together in women with HER 2 positive breast cancer who have had their tumors completely removed by surgery.

Impovements in adjuvant therapy include extending the length of therapy, addition of taxanes to anthracycline-based regimens, changes in dosing schedules and dose-dense chemotherapy. Chemotherapy regimens in practice include: FEC x 6 cycles, TC x 6 cycles, Dose dense AC x 4 cycles followed by T x 4 cycles and TAC x 6 cycles, where F=Fluorouracil, E=Epirubicin, C=Cyclo-phosphamide, A = Adriamycin, T = Docetaxel/Paclitaxel.

Prof Abraham also informed that neratinib is an experimental drug, TKI of EGFR and HER 2, with potential antineoplastic activity. Trastuzumab DM1, a next generation treatment, is being evaluated. PARP, or poly (adenocin-disphosphate-ribose) polymerase inhibitors represent new direction in cancer treatment of triple negative breast cancer patients.

Director Research thanked Prof Abraham for the very informative lecture.

(Reviewed by Dr Ullas Batra, Associate Consultant, Dept of Medical Oncology)

CARCINOMA LUNG

Lung cancer is the commonest cause of cancer deaths worldwide. An interactive session on Carcinoma Lung was held at RGCI&RC on March 11, 2010 by Dr Nick Thatcher, Professor of Medical Oncology at the Christie Hospital NHS Trust in Manchester, UK. The session was attended by Dr DC Doval, Director Research, Consultants, Residents, DNB students and Research Officers in the Institute.

Dr Sajjan Singh, DNB student, Medical Oncology, presented the case of a 47-year old male smoker diagnosed as small cell lung cancer (SCLC), limited stage subtype, in August 2007. He had received 6 cycles of cisplatin and etoposide followed by external beam radiotherapy to chest wall. He presented with cough and haemoptysis in December 2009 . Bronchoscopy revealed right upper lobe margin hyperemic, swollen and intermediate bronchus narrowed. Bronchial biopsy suggestive of SCLC and CT chest showed enlarged subcarinal lymph node (3.5 cm).He then received 3 cycles of etoposide and cisplatin. Reassessment with PET-CT showed only metabolically active sub cm subcarinal lymph node with no other site of active disease. The options were (1) To continue chemotherapy till 6 cycles followed by response assessment, (2) Reirradiation to chest, (3) Surgery followed by chemotherapy, (4) Role of prophylactic cranialirradiation (PCI). Prof Thacher suggested continuing chemotherapy till 6 cycles followed by PCI, as it improves survival.

The superior venacava (SVC) serves as the venous drainage for the head, upper limbs and upper thorax and may be extrinsically compressed by middle and anterior mediastinal masses. SVC obstruction(SVCO) consists of a symptom complex. Dr Kumar Deep, DNB student, Medical Oncology, presented the case of a 45-year old female, non-smoker with complaints of productive cough, breathlessness and jaundice with increased breathlessness and cough for one day. On examination, performance status was 4, pallor and icterus with pedal edema, engorged neck and chest veins. Bilateral crepts, air entry in left side was decreased and liver was palpable. Bronchial biopsy: Non small cell (NSC) undifferentiated carcinoma. Fine needle aspiration cytology (FNAC) of left supraclavicular node showed metastatic poorly differentiated carcinoma. Pleural fluid cytology showed no malignant cell. Outside slide review: Adenocarcinoma. PET- CT chest and abdomen revealed wide spread disease. The final diagnosis was right upper lobe mass (adenocarcinoma) with SVCO and adrenal metastasis. The options were (1) Best supportive care, (2) Palliative chemotherapy, (3) Palliative radiotherapy (RT) lung mass followed by chemotherapy, (4) SVC Stenting followed by palliative chemotherapy. Prof Thatcher suggested for SVC stenting followed by RT.

Dr Ullas Batra, Associate Consultant, Medical Oncology, reported the case of a 56-year old, non-smoking male, who presented with complaints of cough and breathlessness since 3 months. CT chest revealed a 4x3.5 cm right upper lobe lung mass with multiple bilateral pulmonary nodules and lymph nodes and pleural effusion. Physical examination revealed a right sided pleural effusion. CT guided trucut biopsy of lung lesion : NSCLC, adenocarcinoma subtype. PET scan revealed widespread disease with multiple skeletal metastases. He received pemetrexed and carboplatin based chemotherapy. Reassesment following 3 cycles of chemo showed near complete response in lung and bone lesions and complete response after 6 cycles. Prof Thatcher suggested that pemetrexed can be continued for maintenance therapy which improves survival.

For concurrent chemoirradiation, etoposide and carboplatin should be followd by surgery, and adjuvant chemotherapy if the disease is positive after resection. He said that postoperative radiotherapy for N2 disease shows no benefit.

Lesion in the apex of lung, associated with specific symptom complex is called "Pancoast" (Superior sulcus) tumor. Neoplasm in this location may invade the structures in the thoracic inlet. Dr P Suresh, DNB student, Medical Oncology, presented a 50-year old male patient with complaints of cough and pain in right shoulder. CT chest showed pancoast tumor with destruction of right 1st and 2nd rib with chest wall involvement. FNAC: NSCLC. No other site of metastasis found. The patient received preoperative chemoradiotherapy with 45 Gy radiotherapy. After re-evaluation, residual disease was present and complete resection with negative margin was unlikely. Prof Thacher suggested that optimal dose of preoperative radiotherapy is 60 Gy and the patient can be given 3 more cycles of chemotherapy, preferably gemcitabine based because of squamous cell subtype.

Director Research thanked Dr Thatcher for the visit to the Institute and the interactive session was well appreciated by the audience.

ADRENAL LESIONS & IMAGING

Dr Gopal Vijayaraghavan, Associate Director, Abdominal Imaging at the Department of Diagnostic Radiology, University of Massachusetts Medical School, Worcester, USA, visited RGCI&RC on April 5, 2010 and delivered a lectutre on "Common Adrenal Lesions and Mimickers on Imaging".

Remarkable progress has been made in elucidating the structure and function of adrenal gland since the time of Thomas Addison. It is mainly an endocrine organ composed of cortex (90%) and medulla (10%). Adrenals are located near the upper pole of both kidneys. On CT, the adrenals are normally 4-5 cm long and the limbs are 5-7mm thick.

Imaging of Adrenal Gland

Imaging modalities are plain films, ultrasound, CT, MR, nuclear scintigraphy, PET, angiography and needle biopsy. Plain films are of limited use and angiography is rarely required now a days. CT is the most readily available and consistently effective means of imaging the adrenal gland. CT is performed using 3-5mm collimation, before and after IV contrast administration with dilute oral contrast agents. Delayed images are taken at 10/15 minutes for "wash out" patterns. Various MR imaging parameters, including T1 and T2 characteristics, enhancement patterns, and chemical shift characteristics can be used to characterize adrenal masses primarily to differentiate benign from malignant diseases. Radiolabelled analogue of cholesterol and I^{131} MIBG are used for workup of suspected adrenal cortical and medullary disease, respectively. Recently, PET-CT has shown promise in differentiating benign from malignant mass with high sensitivity, specificity and overall accuracy for detecting adrenal metastasis.

Adrenal Masses

Commonly encountered adrenal masses are adenoma (functioning & nonfunctioning) and metastasis. Other uncommon masses are pheochromocytoma, adrenal cortical carcinoma, neuroblastoma, hemorrhage, myelolipoma/lipoma, cysts and granulomatous infection.

Adenomas are characterized by presence of intracellular lipid with unenhanced CT attenuation of <10 HU, unique early enhancement and early washout of the contrast. An absolute contrast washout of >60% and a relative contrast washout of >50% characterize an adenoma with a sensitivity and specificity of 98 % and 92%, respectively. It is never seen in metastasis/ adrenal cortical carcinoma/pheochromocytoma. Recently, there is an increasing role of chemical shift MRI.

Metastasis to adrenal gland can arise from carcinoma of the lung, breast, lymphoma or melanoma. Metastases are irregular and often bilateral with attenuation values of >10 HU on unenhanced scan and have <60% absolute and <40% relative contrast washout. MRI shows higher signal on T2WI. Pheochromocytomas are catecholamine producing tumour arising from ganglion cell anywhere in autonomic nervous system. Ninety percent cases arise in adrenal medulla while 10% cases are bilateral, extra adrenal and malignant. CT shows as >2 cm mass with homogenous enhancement and rarely cystic. MRI reveals hyperintensity on conventional T2WI. MIBG scintigraphy is problem solving tool in adrenal, extra adrenal and metastatic disease. Adrenal cortical carcinoma is a rare primary adrenal malignancy, often >6cm in size with heterogeneous enhancement and 30% contain calcification while 10% are hyperfunctional. They are locally invasive and metastasize to liver, lung and bone.

Dr Vijayaraghavan described incidentalomas as incidentally discovered <3 cm adrenal masses in patients with no history of malignancy, likely benign and extensive work up not justified. Endocrinological work up should be considered since subclinical hyperfunction is present in 5% of incidentalomas. If work up deemed clinically important, CT or Chemical Shift MRI should be considered. Lesions 3-5 cm in size should be followed up with CT/CSI/adrenal biopsy. Lesions > 5 cm should be removed because of risk of malignancy. Myelolipoma/ lipoma (fat in CT and MR), neuroblastoma (pediatric adrenal mass with calcification) and adrenal cysts are seen rarely.

Mimickers of adrenal lesion include gastric diverticula, splenic artery aneurysm, splenorenal collaterals, exophytic renal angiomyolipoma, pancreatic pseudocyst etc.

Conclusion

With the widespread use of cross-sectional imaging, detection of asymptomatic adrenal masses has increased. Recent advances in imaging technology have helped in characterizing most of the lesions non-invasively. However, a few of the equivocal cases still require cytopathological examination for confirmation.

(Dr Padma Talukdar, DNB student; Dr AK Chaturvedi, Chief, Dept of Radiology & Medical Director)

RGCON-2010: HIGHLIGHTS

RGCON-2010, the 9th Annual International Conference was organized by Rajiv Gandhi Cancer Institute & Research Centre from 25th-28th March 2010. The theme of the conference was ***"Strategies for Preservation of Organ Structure and Function in Cancer."***

Four different, but related activities had been planned under the umbrella of RGCON-2010: A **RGCON-2010 Symposium** on "Strategies for Preservation of Organ Structure and Function in Cancer and Implications for Global and National Cancer Control Programmes" on 25th March'10; **RGCON-2010 CME** on "Molecular Biology Techniques in Cancer Diagnosis and Treatment" on 26th March 2010; **RGCON-2010 Workshop** on "How I Do it?" on 26th March 2010 and finally, the **RGCON-2010 Conference** on 27th and 28th March 2010.

RGCON-2010 Symposium was a curtain raiser to the main event and was intended to focus on the Global and National Cancer Control Programmes, undertaken by the various National and International agencies. Its purpose was to evolve policies to overcome the resource gap that appears to be a major rider in providing adequate treatment facilities, capacity building and trained manpower to tackle this global epidemic, especially in developing countries that have limited resources.

The symposium was inaugurated by Dr Yonas Tegnen, Scientist and Public Health Administrator, World Health Organization (WHO), India, and was addressed by various officials from WHO, Ministry of Health & Family Welfare, Govt of India, UICC, C-DAC, National Cancer Institute, Cairo, medical professionals from major Institutes like AIIMS, TMH, etc, various firms involved with the manufacture of teletherapy equipments from both governmental (M/s SAMEER, Panacea) & private organizations (M/s Siemens, Varian, Elekta & Theratronics). Representatives from NGOs, like Cancer Sahayog and Indian Cancer Society also participated in the deliberations. The opening address of the symposium was delivered by Prof PC Joshi, a 82-year old patient who had been successfully treated for cancer using organ preservation strategies. He shared his feelings as a patient before the delegates, the various thoughts that went through his mind when he was diagnosed of cancer, his struggle to fight the disease and now after "crossing the dark tunnel." It was an extremely emotionally charged thought provoking talk that touched the hearts of the 120 delegates attending the symposium.

RGCON-2010 CME on "Molecular Biology Techniques in Cancer Diagnosis and Treatment" was to motivate the early level graduates, postgraduates and research scholars in biomedical sciences, biotechnology, life sciences, microbiology, genetics and biochemistry to pursue basic research in cancer. It was also to update the clinicians, especially the residents on the various aspects of molecular biology, as these techniques are gradually getting integrated into the clinical practice and could form an integral component of translational research in oncology.

The opening remarks by Dr Joe Y Chang, an eminent scientist at MD Anderson Cancer Center, USA were greatly appreciated. Prof SS Agarwal, Ex Director, ACTREC and SGPGIMS delivered the key note address, entitled 'Overview of Molecular Biology of Cancer" which provided an apt start to the whole CME. This was followed by presentations by eminent speakers on blotting assays and PCR, in situ hybridization methodologies, DNA microarray and microRNA in cancer. The presentations were followed by an avid discussion with a very interactive audience. The CME was a huge success owing to the keen interest taken by both the faculty and the 116 participants who attended the CME.

RGCON-2010 Workshop was conducted on 26th March 2010 and was based on the theme "How I Do It?" It was planned to provide a learning opportunity of various state-of-the-art surgical and radiation oncology techniques from the experts, both National and International, who have been performing these procedures. The various cancer sites that were covered included pancreatico-hepatobiliary, lung, head & neck, breast and prostate. A number of International and National faculty members discussed these techniques. Each of the session concluded with a very interactive session with active participation from the delegates. Around 225 delegates attended this workshop.

RGCON-2010 Conference was designed to bring out the latest advances in the multimodal management of cancers, highlighting the theme of the conference. Keeping in view the multimodality treatment approach in cancer directed towards organ structure and function preservation, a forum was provided to discuss the various possible options of tackling this disease and discuss the evolving strategies to provide an improved

Dr AK Chaturvedi, Medical Director and Ms Jyotsna Govil, Hony. Secretary, RGCI &RC; Dr MCS Bermedo, Senior Adviser, Cancer Control, WHO, Geneva; Ms Sujatha Rao, Secretary (Health), MOH&FW, Govt of India; Dr KV Swaminatahan, Chairman and Shri DS Negi, CEO, RGCI&RC

quality of life without compromising the cure. Thus, apart from lectures, a number of debates had been included to have a scientific exchange of thoughts and explore the best possible amalgamation of the various allied specialties that could be practically useful. The conference also provided enough opportunities to residents and trainees to express their views and interact with the leading experts in their respective fields.

RGCON-2010 conference was inaugurated by Ms Sujatha Rao, Secretary (Health), Ministry of Health & Family Welfare, Government of India. The "Guest of Honour" for this occasion was Dr (Ms) Maria Cecilia Sepulveda Bermedo, Senior Adviser, Cancer Control, World Health Organization, Geneva. The RGCON-2010 Souvenir and the RGCON-2010 Proceedings were both released on this occasion. Two prestigious awards instituted by RGCI&RC were given at the inaugural function. To encourage high quality publications, the Institute conferred the "Dr PS Raman Memorial Prize" to Dr Gauri Kapoor, Senior Consultant, Dept of Pediatric Hematology & Oncology, RGCI&RC, for her paper entitled "Application of SNaPshot for analysis of thiopurine methyl transferase gene polymorphism", published in *Indian Journal Medical Research*. Dr Preeti Bagga, Senior Resident, Department of Radiation Oncology was bestowed with the "Chairman's Young Achiever Award 2009".

Two prestigious orations- "Mr Harish Chandra Bajoria Memorial Oration" and "Dr Raman Chadha Memorial Oration" were delivered by Dr Arun K Kurkure, Member Board of Directors, UICC and Senior Oncosurgeon, Breach Candy Hospital, Mumbai and Prof GK Rath, Chief, IRCH & Head, Department of Radiation Oncology, AIIMS, New Delhi, respectively. While Dr Kurkure spoke on "Role of modern surgical oncology techniques in preservation of organ structure & function in cancer", Prof Rath gave a lucid presentation on "Role of modern radiation oncology approaches for organ structure and function preservation in cancer".

One of the major highlights of this year's RGCON-2010 was a number of debates. The topics of the debates were related to the problems in the decision making for some of the common clinical conditions in sites, including head & neck, oesophagus, prostate, bladder and rectum. Speakers from surgical and radiation oncology were either asked to speak either "For" or "Against" the motion, depending on the statement of the debate. The debates were very well moderated by a panel of chairpersons representing surgical, medical and radiation oncologists. Even the house was given an opportunity to vote at the end of a debate. It was evident from all these debates that more than 80% of the delegates were in favor of organ preservation strategies in all these sites, that should be practiced without compromising on cure rates.

The resident delegates had an opportunity to compete for the **"Most Promising Oncology Resident Award."** The competition was carried out in multiple stages, with first scoring on blinded abstracts and then poster presentations. Based on the summated scores of abstracts and posters, 6 shortlisted residents were invited for an oral presentation. Dr Pooja Khullar, DNB student, Department of Radiation Oncology, RGCI&RC, won the 3rd prize in this competition. Apart from this, to encourage an interaction by the residents, every session had prizes for the **"Best Interjector Prize"** based on the type of questions / discussions that were raised by the residents. It was quite a keenly contested event, and was intended to encourage a good and lively participation from the residents.

Thus, the 4-day event of RGCON-2010 came to a close on 28th March 2010. A total of 744 delegates attended this event. This included delegates from USA, Austria, Japan, China, Nepal, Bhutan, Fiji Islands and various parts of India. Based on the analysis of the feedback responses (online & hard copies) submitted by the delegates (National & International), it was apparent that RGCON-2010 was well appreciated by all the delegates, especially for its academic content, which was the primary purpose of this event.

(Prof N R Datta, Sr Consultant & Co-ordinator, Dept of Radiation Oncology)

CASE REPORTS FROM RGCI&RC

PERSISTENT MULLERIAN DUCT SYNDROME WITH TESTICULAR TUMOR

Case Summary

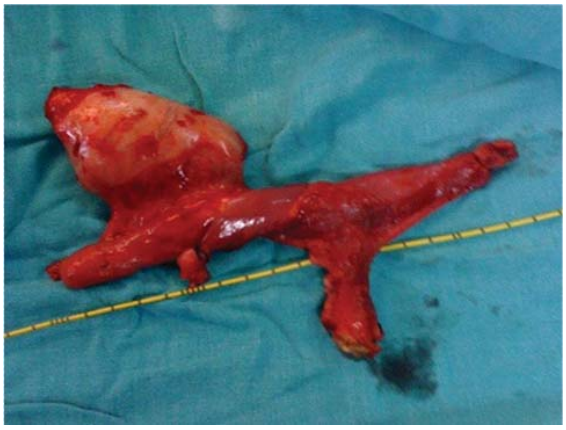
A 34 years old male presented in August 2009 with history of bilateral undescended testis since birth, abdominal distention since one month and right lower limb swelling since four days. He had past history of left orchiopexy 10 years back. He has been married for three years but doesn't have any child.

On examination, his vitals were stable. There was a palpable abdominal lump 10x10 cm in right lumbar region and 3x3 cm mass in right iliac fossa. Both scrotal sacs were empty. Chest, cardiovascular system and central nervous system examination were normal.

Investigations revealed the levels of tumor markers as: AFP - 0.539 ng/ml, β-HCG - 2.95 mIU/ml, LDH-4670 U/L. CT chest/ abdomen showed multiple enlarged retroperitoneal lymph nodes, including retrocaval, para-aortic, iliac nodes encasing the right common iliac vessels, heterogeneous soft tissue mass in right external iliac region inseparable from nodes and 2.2x5.8 cm nodule in right upper lobe of lung. Venous Doppler of lower limbs showed right ileofemoral venous thrombosis. So he was considered high risk for surgery and hence planned for chemotherapy. CT guided fine needle aspiration cytology from retroperitoneal mass was suggestive of seminoma. Patient denied for his semen analysis and preservation.

He received 3 cycles of BEP (bleomycin, etoposide and cisplatin) regimen of chemotherapy drugs from August 15 to September 30, 2009. Post treatment examination revealed persistent right lower limb swelling. The levels of tumor markers were as follows: AFP - 2.47 ng/ml, β-HCG - 0.18 mIU/ ml, LDH - 507 U/L. CT chest was normal and CT abdomen showed confluent nodes in retroperitoneal and right external iliac mass. PET-CT on October 09, 2009 showed right external iliac mass with calcification showing heterogeneous tracer uptake, heterogeneous uptake in confluent lymph nodes with both lungs normal.

Patient underwent retroperitoneal nodal dissection on November 09, 2009. Pre-operative findings were intra-abdominal ovotestis with mullerian duct remnant



Specimen: Mullerian duct remnants with right testis

showing fallopian tube with fimbriae, abdominal vestigeal uterus entering into prostatic utricle. Dense desmoplastic reaction was observed in the retroperitoneum. Pathological examination showed no evidence of seminomatous tissue and fibrosis with desmoplastic reaction.

Discussion

Persistent Mullerian Duct Syndrome (PMDS) is an uncommon disorder in men. They have testis and male phenotype with bilateral fallopian tubes and uterus. It is caused by deficiency of mullerian inhibiting factor (MIF). MIF gene has been linked to chromosome 19. Less than 20 cases of PMDS and testicular tumor have been reported so far. All these cases were reported post-puberty with the commonest histology being seminoma. The overall incidence of malignant transformation is 15%, similar to abdominal testis in normal men. Mullerian remnants are not palpable abdominally or per rectal examination and are diagnosed only by surgical exploration. Malignant degeneration in PMDS tissues has not been documented and mullerian remnants are rudimentary. Removal of these structures during surgery is not mandatory. For management, staging and treatment policy is similar to that of scrotal testicular tumor.

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VISCERAL LEISHMANIASIS MIMICKING ABDOMINAL LYMPHOMA

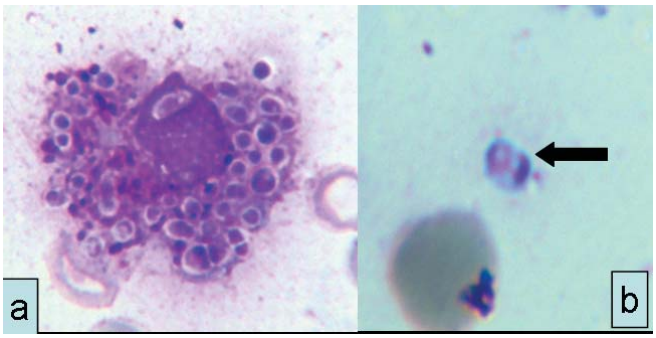
Case Summary

A 16 months old boy, resident of Manipur presented with **history** of fever on and off for 6 months, high grade persistent for the past 3 weeks. It was associated with anorexia and irritability. **Examination** revealed a pale, malnourished child with abdominal distension and no organomegaly or free fluid. Complete blood count revealed Hb-6.9gm %, WBC- 8970/cumm and platelet count-2.48 lakhs/cumm. Abdominal imaging (sonogram and CT scan) revealed presence of multiple mesenteric and retroperitoneal lymphnodes encasing the mesenteric vessels. Child was referred as a case of abdominal lymphoma to RGCI&RC. An image guided FNAC was done from mesenteric lymph nodal mass which showed a mixed population of inflammatory cells comprising eosinophils, histiocytes and lymphoid cells. Many histiocytes showed multiple intra cytoplasmic bodies lying in a vacuole and possessing dual chromatic structures, suggestive of Donovan bodies (see Fig). The **pathology report** clinched the diagnosis of visceral leishmaniasis.

The child was **treated** with liposomal amphotericin B at a dose of 2.5 mg/kg/day for seven consecutive days and then on day 14 to complete a total cumulative dose of 20 mg/kg. His fever gradually subsided, appetite improved and abdominal distension subsided.

Discussion

Leishmaniasis is a disease caused by the protozoa of the *Leishmania* species and transmitted by the bite of a female sandfly. It is classified as cutaneous, mucocutaneous, and visceral leishmaniasis ('Kala Azar'). Ninety percent of the visceral leishmaniasis cases occur in Bangladesh, Brazil, India, Nepal and Sudan. It is endemic in North East (North Bihar), West Bengal and eastern UP. The amastigotes replicate in macrophages of the mononuclear phagocyte system and spread to the reticuloendothelial system causing 'Kala Azar'. It is the most devastating form of the disease and if left untreated can be fatal. In developing countries young malnourished children are extremely susceptible to develop progressive infection. Common signs and symptoms include intermittent fever (95%), pallor (77%), refusal to feed (40%), weight loss (18%), abdominal distension (18%), cough (16%), vomiting (15%) and diarrhea (12%); massive splenomegaly (99%), hepatomegaly (85%), lymphadenopathy (39%) and bleeding (2%)[1]. Common laboratory findings include anemia, neutropenia, thrombocytopenia, hypergammaglobulinemia and hypoalbuminemia[2]. The parasite can be demonstrated for definitive diagnosis on bone marrow aspirates, splenic or lymph node aspirates. In immunocompetent individuals serological assays (direct agglutination, indirect immunofluoroscence, K39) are considered to be sensitive.



High oil, giemsa stain demonstrates (a) a macrophage with numerous LD bodies (b) exhibits an extracellular amastigote form with dual chromatin

Differential diagnosis of visceral leishmaniasis includes malaria, tropical splenomegaly syndrome, tuberculosis, leukemia and lymphoma. It might mimic certain malignancies and a tissue diagnosis is essential for its diagnosis. The management of each patient depends on correct diagnosis and efficacy and toxicity profile of the drugs and also on the host factors.

For more than half a century, sodium stibogluconate was the standard of care but during the past decade, the high failure rates (upto 60%) of this compound has led to its abandonment as first line drug. Currently, Amphotercin B and its lipid formulations have been proven to be highly active against visceral leishmaniasis in India with long term cure rates of 90-95%[3]. Lipid formulations are to be given in the dose of 3 mg/kg/day on day 1-5, 14 and 21. Oral treatment has become a reality with introduction of Miltefosine in dose of 2.5 mg/kg/dose qid for 28 days[4].

References

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