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Printed and Published by  
 Rajiv Gandhi Cancer Institute &  
 Research Centre, Sector - 5  
 Rohini, Delhi - 110085

*From the Desk of Director Research*

Personalized medicine in cancer is the use of in-depth biologic information about an individual patient to make decisions about the care. It represents a tremendous potential for prevention and early detection of cancer and improvement of the effectiveness and tolerability of therapy. "Special Feature" in this issue highlights 'Era of Personalized Medicine in Cancer'.

Figuring out the right treatment for the right patient requires well designed clinical trials and co-development of biomarkers. Our special thanks are due to Dr Arun Bhatt, President, Clininvent Research, Mumbai for contributing an article on 'New Paradigm for Drug Development in Oncology'.

Nanoparticles have shown a bright future as a new generation of cancer therapeutics. "Perspective" in this issue profiles 'Nanoparticles: Cancer Therapy'.

Health related quality of life (QoL) is a major area of concern in the treatment of patients with cancer. QoL has become an essential tool in cancer management. "In Focus" covers 'Quality of Life Issues in Oncology'.

Other regular features covered in this issue are "Research & Development", "New Technologies", "Clinical Trials", "Watch Out" and "Globe Scan".

RGCON-2011, an annual International Conference was organized by the Institute from 4<sup>th</sup>-6<sup>th</sup> February, 2011 with the theme "Malignancies in Childhood". A brief coverage of the conference is reported in this issue.

A special thanks to Abbot Health Care Pvt. Ltd for sponsoring this issue of Cancer News. We also gratefully acknowledge the contributions made by Clinicians, Scientists and DNB students of the Institute.

Views and suggestions from our readers are welcome.

*Dr D C Doval*

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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.

Printed at  
 Sagar Printers &  
 Publishers,  
 1880 Udaichand Marg,  
 Kotla Mubarakpur,  
 New Delhi - 110 003

## SPECIAL FEATURE

### ERA OF PERSONALIZED MEDICINE IN CANCER

#### Introduction

While choosing the therapy of every diagnosed cancer patient today, we usually rely to use agents and approaches based on the results known among groups of patients. The individual patient's unique biological data, and his personal characteristics are seldom used in arriving at a treatment decision. All this is about to change in a profound way and, we will be in the era of "personalized" medicine in cancer, sometime in the future.

The tools for characterizing individual biology with high throughput proteomics, genomics and kinomics, are getting cheaper and more accessible by the year. These, coupled with the understanding of the biology and molecular pathogenesis of common cancers, are key to the new paradigm of cancer care. Oncologists will say to their patients that "your cancer is unique to you, and must be treated differently!"

Where do we begin? First of all, we put the patient first in everything we do, and always make cancer care personalized care. Then we ask the patient his personal preferences, as to what toxic effect he or she is willing to accept as a trade off for relief, or remission or cure. Incorporating patient preference in the treatment plan, is not only the cornerstone of evidence based medicine but also the foundation of personalized medicine. A woman who has a family history of osteoporosis is likely to choose tamoxifen for her breast cancer while the one at greater risk for endometrial cancer, will choose an aromatase inhibitor for the same indication. Risk determined by the BRCA 1 and 2 mutations are also examples of discovery on the management of a heritable cancer of the breast.

All the agents and procedures, beginning with nitrogen mustard approved in 1949, to panitumumab in 2009, are results of the "watch and wait" policy of cancer care ("if it has worked in a study, it probably will, but let us watch"). Getting to know the patient's genome and then proteome, really started in 2000 when the entire human genome was sequenced, and presented to humanity. There has been a wellspring of hopeful predictions about the impact of informed medical care on individual

patients. The Cancer Genome Atlas (TCGA) published by the US National Cancer Institute in 2005, and the Oncology Biomarker Qualification Initiative (OBQI) of the US Food and Drug Administration, which help develop the process of drug development, have given an impetus to the process of searching for targeted, personalized therapies for a variety of malignancies.

The objectives of the personalized cancer care plan include:

1. Determining the chances that a person will develop cancer and selecting screening strategies to lower risk.
2. Matching patients with treatments that are more likely to be effective and cause fewer side effects.
3. Predicting the risk of recurrence.

The holy grail of cancer therapeutics has been finding a way to kill cancer cells without affecting a patient's normal cells. Toxic chemicals like nitrogen mustard and arsenic have not achieved this objective, but the cytotoxic agents of eighties and nineties (doxorubicin, paclitaxel) have achieved this with a fairly safe therapeutic index.

Biological targeted compounds (imatinib for chronic myelogenous leukemia) and trastuzumab for a subset of breast cancers are paradigms of "targeted therapy", where only cancer cells are killed, leaving normal cells intact. This approach of course needs a target on the cancer cell, like the bcr/abl tyrosine kinase domain in the CML cell, or the Her2 extra cellular domain in the breast cancer cell.

The last five years have in fact seen a host of ethnic, biological, molecular and epigenetic features of cancer cells being characterized, resulting in a plethora of approaches potentially useful in the treatment of cancer. Cancer is now increasingly recognized as a "pathway disease". Pathways to proliferation, apoptosis, metastasis, angiogenesis and anaplasia are all present in the wire mesh of enzymatic structure of the cancer cell. Each targeted drug, or antibody or small molecule (peptide) actually acts like a key on the lock of a pathway to programmed cell death (apoptosis), so that cancer cell stops growing in its uncontrollable fashion, and instead is hurled into the abyss of programmed self destruction.

Targeted therapies are developed by means of what is termed "translational research". This approach differs from conventional oncology in that the drugs are designed after the target is identified. In this new branch of oncology, the search for evidence that a given drug

works on a specific target starts very early in drug development, until “proof of principle” drugs are found effective.

Gene profiling is starting to become part of the treatment plan for some patients. For example, the Oncotype DX evaluates 21 genes to predict recurrence in women with early stage (I and II), node negative, ER positive breast cancer. The test indicates “low, or intermediate or high” recurrence score for breast cancer, and helps determine if the given patient needs adjuvant chemotherapy.

Targeted imaging, or “molecular imaging”, is aiding this revolution in personalized cancer care. For example, choline peaks on the MRI denote the malignant nature of the tumor.

The response criteria of tumors treated with the targeted treatments are different. The usual terms of assessment like partial response, stable disease, or non-response, are not applicable to cancers treated with targeted therapy. The tumor may or may not actually shrink, but the host lives relatively symptom-free.

The conventional method of testing new drugs in comparison to the standard of care always involved a randomized clinical trial. The characteristics of patients within a given arm of a trial, always varied. The major paradigm shift after the discovery of molecular targets, is that now the number of subjects necessary to recruit in a clinical trial has become biologically defined, and smaller. These biologically “enriched” study populations

within a clinical trial, are better able to define responses to newer therapies, because they are pre-selected for a given biological cancer characteristic. For example, the IPASS trial clearly identifies the benefit of tyrosine kinase inhibitors in lung cancer patients whose tumors expressed mutated EGFR, more importantly, as tyrosine kinase inhibitors in fact are deleterious to patients without such mutations in their tumors.

Diagnosing cancer means undergoing a biopsy. However, the detection of “circulating tumour cells” will in fact make cancer diagnosis simpler and non-invasive. The cost of current targeted cancer therapies is high. However, as data regarding their efficacy matures, the intellectual property rights of these discoveries are certain to change hands, and become available to large populations of patients needing them.

**Pharmacogenomics**

The individual patient has unique proteins in either excess or deficient, and this characteristic determines the rate of metabolism (clearance) of certain anticancer drugs. Polymorphism of certain gene allele, from one or both parents, will determine the amount of an enzyme which is available for metabolizing the drug. For example, the enzyme thiopurine methyl transferase (TPMT) metabolises the drug 6-mercaptopurine, in acute lymphoblastic leukemia.

Eighty-six percent of normal individuals possess both alleles for the production of this enzyme (are homozygous). They are able to metabolise

**Table: Some Personal Characteristics which Determine the Efficacy of a New Cancer Treatment**

Mutations	Abnormality	Function	Therapy	Disease
Tyrosine Kinase Domain	Bcr-abl	Proliferation	Imatinib	CML
	c-kit	Proliferation	Imatinib	GIST
	PDGFR	Proliferation	Imatinib	HES
EGFR Domain	Her2	Proliferation	Trastuzumab	Breast cancer
			Lapatinib	
EGFR	EGFR	Proliferation	Gefitinib	NSCLC
EGFR	EML4-ALK	Proliferation	Erlotinib	Adenocarcinoma
EGFR	PML-RAR-α	Anti-apoptosis	Crizotinib	NSCLC
Retinoic Acid	CD 20 expression	Proliferation	ATRA	APML
			Rituximab	NHL
BCL-2 Overexpressed		Anti-apoptosis	Oblimersen	NHL
Cyclin D Overexpressed		Prevents apoptosis	Bortezomib	MCL
Multitargeted (VEGF/EGFR/PDGFR)		Prevents apoptosis	Sunitinib	RCC
Multitargeted Mutations		Angiogenesis	Bevacizumab	mCRC
			Sorafenib	RCC
VEGF Expression		Angiogenesis	Vatalanib	NSCLC
mTOR Pathway		Transcription	P1103	NSCLC
P13k		Signal transduction		

EGFR, epidermal growth factor receptor; Bcl-2, B-cell lymphoma 2; VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptors; mTOR, mammalian target of rapamycin; PI3k, phosphatidylinositol 3-kinases; bcr-abl, breakpoint cluster region-abelson; Her2, human epidermal growth factor receptor 2; EML4-ALK, echinoderm microtubule-associated protein like 4-anaplastic lymphoma kinase; PML-RAR-α, promyelocytic leukemia gene-retinoic acid receptor alpha; CD 20, cluster of differentiation 20; ATRA, all trans retinoic acid; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumors; HES, hyper eosinophilic syndrome; NSCLC, non small cell lung cancer; APML, acute promyelocytic leukemia; NHL, non-Hodgkins lymphoma, MCL, mantle cell lymphoma; RCC, renal cell carcinoma; mCRC, metastatic colorectal cancer

6-mercaptopurine, and are able to tolerate the drug well. Eleven percent, however lack one of the alleles, and are "heterozygous". Three percent individuals lack both the allele, and are completely deficient in TPMT. If these individuals are given 6-mercaptopurine, as treatment for acute lymphoblastic leukemia, then they are likely to suffer from life threatening neutropenia. It is therefore important to determine the mutational status of TPMT gene.

The enzyme UGT1A1A determines the rate of metabolism of Irinotecan in colorectal cancer and determines the efficacy and /or toxicity of the drug.

The individual deficiency in the cytochrome oxidase enzyme CYP2G6 is likely not to process tamoxifen well, and has a greater risk of breast cancer recurrence.

### Pharmacoeconomics

The economic status of the individual is a very important factor in determining access to care, ability to pay for therapy, ability to understand and comply with the requirements of treatment, and finally to cope with the outcome of treatment.

Diversity of races, religions and social mores influence these adaptations to diseases. Therefore, knowing the individual patient and his background cultural values and the economic status, during the initial history, and interview, go a long way to determine the compliance, coping and the final outcome of cancer care.

An oncologist thus, should learn about his patient as a person, before or during the process of knowing the tumor's characteristics. This fore-knowledge will go a long way in furthering his efficacy as a physician in cancer care.

Every once in a while, in a developing country like India, we come across situations of complexity where delivering cancer treatment, or even palliation, requires intimate knowledge of the patient's lifestyle, like his marital status, his family composition, his dependence on other members of the family for finance, and so on. An elderly widow with epithelial ovarian cancer who has no caregiver at home would need a completely different approach as compared to a young tech-savvy executive with testicular cancer, who has his family to take care of "ancillary" aspects of his treatment. The lady in question should be prescribed medication which would minimize the number of visits to the hospital as compared to the young executive, who for reasons of curability of his

cancer, and the abundance of support available at home, should be given an aggressive therapy protocol, and is expected to cope with toxicities far better.

The personalized approach to colon cancer screening and early interventions has been proven in a randomized trial. Substantial increase in screening was achieved by providing subjects with personalized mails, and specific material about their needs.

### The Future

The cost of unraveling any individual's entire genome (30000 genes) by high throughput DNA gene expression profiling is approximately US Dollars 30000 today. The costs on techniques of gene expression profiling (to determine if a set of genes are turned on or off), proteomic and kinomic profiling will fall every few months until it will be affordable to large number of institutions and physicians. Thereafter, it is conceivable that individuals can have their own genomes completely mapped and analyzed for disease susceptibility, and drug sensitivity.

The information can be used to choose the most appropriate therapy for that individual's cancer. The technique of micro RNA based detection of cancer biomarkers also is likely to develop into a full fledged science, aiding the processes of personalized medicine. The role of curative cyto reduction by means of debulking surgery or radical radiotherapy is unlikely to disappear any time soon. This approach is likely to remain the principal means to extirpate large cancers. Similarly, the role of cyto toxic chemotherapy also will remain important in cancers which are "responsive". After optimal cyto reduction by conventional means, the targeted agents are likely to be used to keep the malignant behaviour of a given cancer at bay. The ethics and economics of this brave new world will evolve in time.

### Conclusion

Personalized medicine is an era which has now dawned. If we are to harness the full potential of this era, and the curative possibilities it offers, we must first treat the patient in holistic totality, with compassion and care. Then, the individual physician's understanding of cancer as a disease must be based on insights of translational research. The future patient shall have a copy of his genomic information with him, while the future oncologist should have the "pathway disease" as a grail of cancer therapy.

*(Dr (Col) Prakash G Chitalkar, Senior Consultant, Dept of Medical Oncology)*

## GUEST ARTICLE

### NEW PARADIGM FOR DRUG DEVELOPMENT IN ONCOLOGY

*“We can’t solve problems by using the same kind of thinking we used when we created them”*

*Dr Albert Einstein*

#### Introduction

The pharmaceutical industry is facing a crisis in research and development of new medicinal entities (NMEs). The cost of drug discovery and development has increased exponentially to US \$ 1.7 billion.<sup>1,2</sup> The time for drug discovery and development has gone up significantly. However, the productivity of the process continues to be under pressure. During past several years, the number of drugs that have received FDA approval, has been going down. In a 2004 study, Kola and Landis found that only 11% of compounds, which entered first-in-human (FIH), were successfully registered.<sup>1</sup> The success rates for CNS and oncology agents were lower, i.e. 5-8%. Major causes of failure have been lack of efficacy and unacceptable toxicity. Late stage failures are common; Phase III accounts for 43% and registration accounts for 23%. In another study, for oncology compounds, 80% of Phase III failures were attributed to efficacy.<sup>1</sup> These late stage failures in efficacy are of major concern and suggest the need for innovation—a paradigm shift in drug development.

#### Critical Path Initiative

US FDA, in 2004, launched the Critical Path Initiative.<sup>2</sup> This was a major initiative that was intended to improve the drug development processes, the quality of evidence generated during development, and the outcomes of clinical use of these products.<sup>3</sup> The “Critical Path” is the process beginning with identification of a new drug candidate and its culminating in approval for marketing. The novel and advanced scientific tools used in drug discovery and lead optimization are generally not utilized in the preclinical and clinical development stages. More often, the drug evaluation has employed traditional empirical approach in both animal and human testing.<sup>3</sup> Sounding the alarm on the increasing difficulty and unpredictability of medical product development, the report concluded that collective action was needed to modernize scientific and technical tools. Major areas

suggested for scientific improvement in the drug development processes were: better development and use of biomarkers, innovation in clinical trial methodologies, and the aggressive use of bioinformatics, including disease modeling and trial simulation.<sup>4</sup>

#### Biomarkers - New Tools for Drug Development

For single anticancer agent Phase I/II trials, drug activity does not always relate to response parameters—the Response Evaluation Criteria in Solid Tumors (RECIST). This means that for early clinical trials, end-points other than tumor size need to be included in the design. Pharmacodynamic (PD) biomarkers, which assess the effect a drug has on the body, can provide a useful indicator of drug activity.<sup>4</sup> For Proof-of-Concept (POC) studies, such PD biomarkers allow the demonstration of intended target modulation and achievement of the desired biologic effects. PD end-points, coupled with pharmacokinetic (PK) parameters, provide a better understanding of dose-response relationship and provide a rational basis for selection of dose regimen.<sup>4</sup> New methods of tumor evaluation, e.g. noninvasive functional imaging and analysis of circulating tumor cells (CTCs) are promising approaches for accelerating the drug development process.

A biomarker can be broadly defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to a therapeutic intervention”.<sup>4</sup> They are sub-classified into other major categories, such as

- Risk biomarkers – prognostic or predictive, e.g. HER2 overexpression in breast cancer
- Biologic progression markers – measurement of tumor burden, e.g. carcinoembryonic antigen (CEA), CA-125 and prostate-specific antigen (PSA)
- PD biomarkers – markers of drug effect

Use of circulating biomarkers, which reflect the biology of the tumor, provides a novel avenue in the drug development. These include circulating nucleic acids, tumor cells and proteomic and metabolomic biomarkers.<sup>4</sup>

The development of a biomarker requires exploratory preclinical or clinical studies for scientific validation followed by laboratory-based technical development.<sup>4</sup> To qualify as a surrogate end point, the biomarker should be modulated by a therapy and correlated with a clinically meaningful end-point. Hence, the development of the drug and biomarker pipelines has to be concurrent.

## Functional and Molecular Imaging

Over the last decade, there has been tremendous progress in new technologies for imaging the effects of cancer drugs. Dynamic contrast enhanced (DCE) MRI, and DCE CT are frequently employed for studying the modulation of tumor vasculature in response to antiangiogenic agents.<sup>4</sup> In addition, the availability of high-resolution scanners, better processing software, and advanced mathematical modeling, has made delineation of various dynamic components of tumor vasculature - blood flow and permeability - possible. Further, PET scanning using radio-labeled tracers is useful in appraising various biologic processes, such as cellular proliferation, tissue perfusion, blood volume and DNA synthesis.<sup>4</sup> The PET has also been applied to evaluation of PK in intratumoral and normal tissue drug and as a PD marker of biochemical modulation. The radiation exposure, cost and labor intensiveness are major disadvantages of imaging biomarkers.

## Novel Clinical Trial Designs

In the wake of FDA's Critical Path Initiative, several new clinical trial approaches are gaining ground. These are: Phase 0 studies, Proof-of-Concept Studies and Adaptive Designs.

### Phase 0 Studies

These are early human studies conducted in small number of subjects, without any therapeutic intent. The objectives of Phase 0 are: (a) to identify potential agents earlier, (b) develop and establish PD assays in human samples before planning larger trials, and possibly (c) cut down the drug development time. The main end-points of such exploratory studies are: (1) assessment of analogues for lead selection; (2) modulation of a molecular target in a tumor in vivo; (3) whole-body imaging for tissue distribution and target binding affinity; and (4) drug PK.<sup>5</sup> Phase 0 trials require a significant investment in development of PK/PD assay. Nevertheless, there is a potential for early and more rational selection of agents for future development as well as the molecular identification of likely therapeutic failures early.<sup>5</sup>

### Proof-of-Concept Studies

During Phase II studies, the focus is on POC study. The design of POC studies would include biomarkers and functional imaging, and the biological expectations of the molecular target agent (tumor shrinkage versus nonshrinkage), the modulation of the target documented

in previous studies (exploratory investigational new drug and Phase I studies), appropriate selection of patients (enrichment studies) and early determination of activity (fluorodeoxyglucose or [18F]-3'-fluoro-3'-deoxy-1-thymidine-PET, dMRI, dCT, sVEGF) for a given target.<sup>6</sup> The end-points would focus on clinical benefit – progression free survival and time to progression – rather than response rate.<sup>6</sup> Establishment of POC early in development has become an important strategy for successful drug development.

### Adaptive Designs

Adaptive trial design is an innovative new tool in the drug development. An adaptive design is defined as a clinical trial design that uses accumulating data to decide on how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.<sup>7</sup> In adaptive design trial, one attempts to learn from the accumulating data and then applies this learning in real-time to modify characteristics of ongoing trial. Trial aspects that could be modified include (but not restricted to) inclusion-exclusion criteria, treatment duration, dose, study end-point, evaluation criteria, randomization, study design, sample size, study hypothesis and statistical analysis plan.<sup>8</sup> As compared to conventional designs, such flexibility is expected to (1) make the study more efficient (fewer subjects, shorter duration), (2) increase likelihood of success of study objective, and (3) yield better understanding of treatment's effect (e.g., better estimates of dose-response relationship or subgroup effects). US FDA's release of 2010 guidance for adaptive design is a major step in encouraging use of this new tool in planning clinical trials.<sup>8</sup>

## Conclusions

Falling productivity in developing NMEs has spurred pharma industry and regulators to look for new paradigms. Use of biomarkers and functional imaging, early assessment of PK and PD in Phase 0 and POC studies, and evolution of adaptive designs offer exciting new strategies to improve selection and development of potential NMEs. These innovations are likely to be the cornerstone of future drug development.

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(Dr Arun Bhatt, President Clininvent Research Mumbai)

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### MAJOR ADVANCES IN CLINICAL CANCER-2010

- **Chemotherapy Combination Increases Survival in Advanced Lung Cancer in the Elderly:** The combination of carboplatin and paclitaxel that is commonly used in younger lung cancer patients proved better than single agent therapy (gemcitabine or vinorelbine) in elderly patients.
- **Chemotherapy Combination Dramatically Improved Survival for Patients with Metastatic Pancreatic Cancer:** Combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin resulted in better response rates, progression-free survival and overall survival compared to standard single drug treatment gemcitabine (Gemzar) in patients with pancreatic cancer
- **Bevacizumab (Avastin) Extends Progression-Free Survival for Women with Advanced Ovarian Cancers:** A Phase III trial found that administering standard chemotherapy (carboplatin and paclitaxel) and bevacizumab, followed by longer-term treatment with bevacizumab, was the most effective strategy.
- **Antibody Ipilimumab Improves Survival in Advanced Melanoma:** Researchers found that ipilimumab resulted in advanced melanoma patients living 34 percent longer after two years.
- **Briefer Course of Radiation Just as Effective in Preventing Recurrence in Early Stage Breast Cancer:** Hypofractionated radiotherapy for early stage breast cancer, comprising a shorter, 3-week course of a higher dose of radiation was just as effective as the standard 5-week course.
- **Novel ALK Inhibitor Shows High Response in Group of Patients with Lung Cancer:** Crizotinib, a specific ALK inhibitor, produced high response rates in a Phase I trial in patients with lung cancer, with more than two-thirds of patients showing some tumor shrinkage.
- **New Targeted Treatment Shows Promise for Advanced Melanoma Patients with BRAF Gene Mutation:** PLX4032, which targets BRAF, showed very high response rates in patients with advanced melanoma and the BRAF mutation (found in about 50% of patients).
- **Adding Palliative Care to Chemotherapy Improves Survival in Patients with Lung Cancer:** A randomized clinical trial of patients with advanced lung cancer showed that individuals who received standard chemotherapy coupled with palliative care immediately after diagnosis lived significantly longer and had a better quality of life than those who received chemotherapy alone.
- **Sleep Problems Impact Large Majority of Cancer Patients Taking Chemotherapy:** In the first large study to evaluate insomnia in patients undergoing chemotherapy, sleep problems were found to affect more than three quarters of these patients, which is nearly three times the rate found in the general population.
- **Sipuleucel-T (Provenge) Approved for Treating Advanced Prostate Cancer:** The US FDA approved provenge, a therapeutic cancer vaccine for metastatic hormone-refractory prostate cancer early in 2010.
- **Cabazitaxel (Jevtana) Approved for Advanced Prostate Cancer:** Cabazitaxel became first chemotherapy for use in advanced hormone-refractory prostate cancer in patients who had failed on docetaxel.
- **Study Reveals Long-Term Risks for Cardiac Problems among Childhood and Adolescent Cancer Survivors:** The investigators found that anthracycline drugs or radiation treatment to the chest increased the risk of cardiovascular problems two to six-fold among survivors compared with those who did not receive anthracycline or chest irradiation.

(J Clin Oncol, Dec 20, 2010)

**PERSPECTIVE****NANOPARTICLES: CANCER THERAPY****Introduction**

Recent progress in cancer nanotechnology has enabled the manipulation of the biological and physicochemical properties of nanomaterials to facilitate more efficient drug targeting and delivery. Nanoparticles, particularly in the range of 10 nm to 100 nm, are emerging as a class of therapeutics for cancer treatment. By using both passive and active targeting therapies, nanoparticles can enhance efficacy and reduce side effects compared with conventional cancer therapeutic drugs. Moreover, nanoparticles offer the potential to overcome drug resistance, since nanoparticles can bypass the P-glycoprotein efflux pump, one of the main drug resistance mechanisms, leading to greater intracellular accumulation. So far, almost all the novel and efficacious nanoparticle delivery systems which have been approved by the FDA or are currently in clinical trials are based on polymer or liposome nanoparticles.

**Nanoparticles**

Nanoparticles used for anticancer drug delivery can be made from a variety of materials, including polymers, dendrimers, liposomes, viruses, carbon nanotubes and metals, such as iron oxide and gold. **Polymers** used for preparation of polymeric nanoparticles can be natural or synthetic. Biocompatibility, biodegradability and their capacity to be functionalized are the requirements. Polymeric particle consists of hydrophobic core which serves as the container for anticancer agents and hydrophilic shell which stabilizes the nanoparticle in aqueous environments. A hydrophobic interaction between the core of the polymeric nanoparticles and the drug molecule allow the drug to be entrapped in the nanoparticle core. **Dendrimers** are synthetic and highly branched with unique features, such as the precise control of size and shape, controlled degradation and the ability to place numerous functional groups on their periphery and/or core. **Liposomes** are spherical particles with a size range of 25 nm to 10  $\mu$ m and a membrane composed of phospholipid bilayers. Drug delivery systems based on unmodified liposomes are limited by their short circulation time and the second generation of polymer coated liposomes can dramatically increase blood circulation times from several minutes up to 3 days.

**Properties**

Four of the most important characteristics of nanoparticles are their size, encapsulation efficiency, zeta potential (surface charge), and release characteristics. A suitable nanoparticle size is very important for efficient drug delivery. Generally, 10~100 nm is considered the optimal size for nanoparticle drug carriers. If the particle size is less than 10 nm, the nanoparticles will be quickly eliminated by renal clearance. At sizes greater than 100 nm, the chance of the particle being captured by the reticuloendothelial system will dramatically increase. A proper surface coating is essential to the stability and circulation time of nanoparticle delivery systems. Generally, a neutral charged nanoparticle can achieve a long circulation time and reduce the chance of nanoparticle capture by the immune system.

**Targeted Delivery**

Nanoparticle delivery of anticancer drugs to tumor tissues can be achieved by either passive or active targeting. Long-circulating therapeutic nanoparticles accumulate passively in solid tumor tissue by the enhanced permeability retention effect (EPR). The hyperpermeable angiogenic tumor vasculature allows preferential extravasation of circulating nanoparticles. The nanoparticles mostly utilize the EPR effect of tumors and the tumor microenvironment to promote their selective delivery to tumors. Active targeting approach is expected to selectively deliver drugs to tumor tissue with greater efficiency. Here, internalization of nanoparticles takes place via receptor-mediated endocytosis. Tumor-specific ligands/antibodies on the nanoparticle bind to cell through an endosome dependent mechanism. Drug loaded particles bypass the drug efflux pump not being recognized when the drug enters cells, leading to high intercellular concentration. Several ligand-targeted therapeutic strategies, including immunotoxins, radioimmunotherapeutics and drug immune-conjugates are being developed. Although these conjugated agents have demonstrated promising efficacy compared with conventional chemotherapy drugs in preclinical and clinical trials, limitations in their delivery efficiency and specificity remain.

**Advances in Cancer Therapy**

Recently, a nanoparticle formulation of paclitaxel bound to albumin (**Abraxane or ABI-007**) was approved for the treatment of metastatic breast cancer. In a Phase III clinical trial, ABI-007 showed greater therapeutic

efficacy and increased response compared with free paclitaxel. Abraxane has also been evaluated in clinical trials involving many other cancers including non-small cell lung cancer (Phase II trial) and advanced nonhematologic malignancies (Phase I and pharmacokinetics trials). N-(2-hydroxypropyl)-methacrylamide copolymer (**HPMA**), polystyrene-maleic anhydride copolymer and polyethylene glycol (**PEG**), are the most widely used nonbiodegradable synthetic polymers. **PK1**, which is a conjugate of HPMA with doxorubicin, was the synthetic polymer-drug conjugate to be evaluated in clinical trials as an anticancer agent. A recent Phase III trial showed that **paclitaxel poliglumex (Xyotax)** was less toxic than free paclitaxel and could prolong the survival of non-small cell lung cancer patients with poor performance status. Also, paclitaxel poliglumex can be used as a novel radiation sensitizer. **Genexol-PM (PEG-poly(D,L-lactide)-paclitaxel)**, a cremophor-free polymeric micelle-formulated paclitaxel has been approved in South Korea.

Currently, several kinds of cancer drugs have been applied to lipid-based system using a variety of preparation methods. Among them, liposomal formulations of the anthracyclines doxorubicin (**Doxil, Myocet**) and daunorubicin (**DaunoXome**) are approved for the treatment of metastatic breast cancer and AIDS-related Kaposi's sarcoma. Many liposomal chemotherapeutics are currently being evaluated in clinical trials. The next generation of liposomal drugs may be immunoliposomes, which selectively deliver the drug to the desired sites of action. A liposomal formulation of cisplatin that lacked efficacy demonstrated encouraging therapeutic results when delivered in an immunoliposome targeted to an internalizing antigen. Recently, promising results were reported from a Phase I clinical study that evaluated the effect of **MCC-465**, a PEGylated liposomal formulation containing DOX targeted with an F(ab')<sub>2</sub> fragment of a human mAb named GAH, in patients with metastatic stomach cancer. Other nanoparticles currently used in the clinic or undergoing clinical trials also showed an improved pharmacokinetic profile compared with the respective free drugs, such as liposomal interleukin 2 (oncolipin), liposomal thymidylate synthase inhibitor (OS1-7904L), liposomal paclitaxel (LEPETU), liposomal lurtotecan (OS1-211), liposomal oxaliplatin (Aroplatin), etc.

During surgery sustained-release delivery devices, such as Gliadel (i.e., carmustine-containing polymeric

wafers), can be implanted into those parts of glioblastoma lesions that cannot be removed surgically. Regarding radiotherapy, preclinical and early clinical evidence suggest that tumor-targeted nanomedicines and radiotherapy interact synergistically with radiotherapy improving the tumor accumulation of the delivery systems, and with the delivery systems improving the interaction between radiotherapy and chemotherapy.

### Potential Toxicity of Nanoparticles

Many candidate polymers have been defined with particular toxicities, such as hematotoxicity, complement activation, carcinogenicity, teratogenicity, and immunogenicity, indicating the importance of choosing safe polymers for the design of nanoparticles. Particular nanoparticles cause increased accumulation of drugs in molecular per se (MPS) cells in the liver, spleen, and bone marrow, with the possibility of increased toxicities to these organs. In addition to hepatic accumulation, some nanoparticles have been reported to cause liver injury (decreased function and hepatic morphology changes). Also, there are safety concerns with particular nanoparticles that are able to cross the blood brain barrier. The failure of MAG-camptothecin due to cumulative bladder toxicity in Phase I trial was also reported.

### Conclusion

Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutic drugs, and have shown a bright future as a new generation of cancer therapeutics. As drug delivery system, nanoparticles have shown an ability to improve pharmacokinetics, pharmacodynamics, efficacy and to reduce the toxicity of associated drugs. There are many limitations to be solved, such as poor oral bioavailability, instability in circulation, inadequate tissue distribution, and toxicity. Multifunctional and multiplex nanoparticles are now being actively investigated. The potential for development of multifunctional "smart" nanoparticles may facilitate the realization of individualized cancer therapy. Although there are many challenges remaining for the clinical development of nanoparticles, as more clinical data are available, further understanding in nanotechnology will certainly lead to more rational design of optimized nanoparticles with improved selectivity, efficacy and safety.

*(Reviewed by Dr Sunil Kumar Gupta, Senior Consultant, Dept of Medical Oncology)*

## RESEARCH & DEVELOPMENT

### Immediate Consequences of Cigarette Smoking

Scientists have reported in a unique study that cigarette smoke begins to cause genetic damage within minutes, not years, after inhalation into the lungs. The results should serve as “a stark warning” to those who are considering to start smoking. Smoking is linked to at least 18 types of cancer. Harmful substances in tobacco smoke, termed polycyclic aromatic hydrocarbons (PAHs), are one of the culprits in causing lung cancer. The first human study investigated human metabolism of a PAH, specifically delivered by inhalation in cigarette smoke. The scientists tracked fate of a labeled PAH, phenanthrene, in 12 volunteers who smoked cigarettes. Phenanthrene quickly formed a toxic substance in the blood known to trash DNA, causing mutations that can cause cancer. The smokers developed maximum levels of the substance in a time frame that surprised even the researchers, just 15-30 minutes after the volunteers finished smoking. The effect was equivalent to injecting the substance directly into the blood stream.

*(Chemical Research in Toxicology, Dec 27, 2010)*

### Lung Cancer Risk Among Tuberculosis Patients

A new study, conducted by the researchers at China Medical University and Hospital in Taiwan, has provided compelling evidence of increased lung cancer risk among people with tuberculosis. They randomly selected one million patients covered under the country’s National Health Insurance Program. For the analysis, they identified 4,480 patients with tuberculosis and 712,392 people without tuberculosis history from a group of 716,872 people. Both the groups were followed for eight years or longer. Results showed that patients with tuberculosis were 10.9 times more likely than non-tuberculosis patients to develop lung cancer (26.3 versus 2.41 per 10,000 person years). Mortality was also much higher in the patients with tuberculosis than in the non-tuberculosis patients (51.1 versus 8.2 per 10,000 person years). The risk of lung cancer may increase further to almost 16 times greater if patients with tuberculosis also suffer from chronic obstructive disease. The study suggests that it is important to watch out for lung cancer prevention in the campaign against tuberculosis.

*(Science Daily, Jan 1, 2011)*

### Pancreatic Cancer Prevention

To find a way to stop early stage pancreatic cancer in research models, researchers at Peggy and Charles Stephenson Oklahoma Cancer Center have shown for the first time that a drug, gefitinib, used in current chemotherapy for later stages of pancreatic cancer had a dramatic effect if used earlier. Gefitinib works targeting signals of a gene that is among the first to mutate when pancreatic cancer is present. This gene is the key in 95 percent of cases of pancreatic cancer. With low doses of gefitinib, which has no known side effects at this level, scientists were able to not only stop pancreatic cancer tumors from growing, but after 41 weeks of treatment, the cancer was gone. The finding points to an effective way to stop pancreatic cancer before it reaches later stages of development where the survival rate drops below 6 percent. This is one of the most important studies in pancreatic cancer prevention and has far-reaching implications in chemoprevention for high risk patients. Researchers hope to begin a Phase II clinical trial, which would focus on at-risk patients, particularly those with pancreatitis, a family history of pancreatic cancer and American Indian populations or others with Type 2 diabetes.

*(University of Oklahoma, Jan 13, 2011)*

### Tasigna for Chronic Myeloid Leukemia

According to new data from Phase III trial, Tasigna (nilotinib) continues to surpass Gleevec (imatinib mesylate) in the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+CML) in chronic phase. With the follow up at 24 months, first line treatment with Tasigna was found to result in a lower incidence of progression to accelerated phase and blast crisis, compared to standard approved dose of Gleevec. Patients receiving Tasigna also had a lower incidence of suboptimal response and treatment failure as defined by study criteria. This 24 months study data extend the evidence of clinical benefit with Tasigna compared to Gleevec. Planned follow up is for five years. Patients on the Gleevec treatment arm who had suboptimal response or treatment failure were allowed to escalate dose and/or switch to Tasigna via a protocol extension. The US FDA and Swissmedic have approved Tasigna in this first line indication. Regulatory submissions are under review in the European Union, Japan and other countries worldwide.

*(Novartis, Dec 8, 2010)*

## NEW TECHNOLOGIES

### DRUGS

#### DAVANAT® for Colorectal Cancer

DAVANAT®, an innovative approach to treating cancer patients, is a polysaccharide polymer that targets galectin receptors on cancer cells and interferes with their activity. Galectins affect cell development and play roles in cancer, including tumor cell survival, angiogenesis, tumor metastasis and give the tumor the ability to evade the immune system. Data from Phase II clinical trial for end-stage colorectal cancer patients showed that DAVANAT® in combination with 5-FU extended median survival by 46% compared with the best standard of care as determined by the patients' physicians. Patients experienced fewer serious adverse side effects of chemotherapy which has the potential to reduce hospitalization and improve quality of life. Pro-Pharmaceuticals, the developer of this drug, has received positive FDA feedback on DAVANAT® Phase III clinical trial design to treat patients with colorectal cancer. It would validate the company's strategy for approach in the US, Colombia and South America in 2011.

*(Pro-Pharmaceuticals Inc, Jan 12, 2011)*

#### Votrient® for Renal Cell Carcinoma

Votrient® (Pazopanib) is a new targeted oral treatment which effectively slows down the progression of advanced renal cell carcinoma (RCC) while maintaining patients' quality of life compared with placebo. It is a tyrosine kinase inhibitor (TKI) and inhibits angiogenesis, thereby slowing tumor growth and the spread of cancer to another part of the body. It has different side effects profile from the other licensed protein TKIs and the side effects are acceptable and manageable. The most frequent adverse events related to treatment were diarrhea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes. The National Institute for Health and Clinical Excellence (NICE) has issued the Final Appraisal Determination (FAD), recommending Votrient as a first-line treatment option for people with advanced RCC who have not previously received cytokine therapy and who are of Eastern Co-operative Oncology Group (ECOG) performance status 0-1 which indicates patient is relatively healthy and well.

*(GlaxoSmithKline, Jan 3, 2011)*

### TECHNIQUES

#### New Tumor-Tracking Technique

Respiratory and cardiac motions induce displacement and deformation of tumor volume in various internal organs. Because of this, radiation oncologists have to irradiate large volumes of healthy tissue and sparing of critical organs adjacent to the tumor becomes difficult. Jefferson's Kimmel Cancer Center researchers have proposed a robotic approach, a novel real-time tumor-tracking technique that could help minimize the amount of radiation delivered to surrounding healthy tissue in a patient, up to 50 percent less in some cases, and maximize the dose the tumor receives. In this technique, the proposed algorithm can predict tumor position and the robotic systems are able to continuously track the tumor during radiation dose delivery. Therefore, a precise dose is given to the moving target while the dose to the nearby critical organs is reduced to improve the patient treatment outcome. According to the study findings, treatment for lung cancer with this technique would result in significant reduction in dose to the healthy tissue, potentially decreasing the probability or severity of side effects.

*(Science Daily, Feb, 2011)*

#### NovoTTF-100A Device for Brain Tumors

NovoTTF-100A, a portable, non-invasive medical device used in a Phase III randomized clinical trial for patients with recurrent glioblastoma tumors for delivering the investigational Tumor Treating Fields (TTF) therapy showed that TTF therapy may increase median survival time and improve quality of life scores compared to best standard of care chemotherapy. The NovoTTF-100A device, which weighs about six pounds, creates a low intensity, alternating electric field within the tumor that exerts physical forces on electrically charged cellular components, preventing the normal mitotic process and causing cancer cell death prior to division. According to the study results, younger patients and patients with better functional status appeared to have an impressive survival advantage. In these patients, the incidence of radiological tumors response to TTF was double of that seen in patients treated with chemotherapy. This therapy also produced significant increase in survival time for patients who had failed treatment with bevacizumab. This therapy is available to patients in Europe and is under review by FDA.

*(NovoCure, Nov 20, 2010)*

## CLINICAL TRIALS

### Bevacizumab in Cancer Patients

Bevacizumab (Avastin), a humanized monoclonal antibody, blocks vascular endothelial growth factor A. It has been approved by US FDA for combination use with standard chemotherapy for metastatic colon cancer, non-small cell lung cancer and metastatic breast cancer. Researchers have conducted a review and meta-analysis of 16 published randomized controlled trials to determine whether bevacizumab is associated with increased rates of fatal adverse events (FAEs) in patients with cancer. A total of 10217 patients with a variety of advanced solid tumors were included in the analysis. Overall incidence of FAEs with bevacizumab was 2.5%. Compared with chemotherapy alone, the addition of bevacizumab was associated with a 1.5 times increased risk of FAEs. This association varied significantly with chemotherapy agents but not with tumor types or bevacizumab doses. Bevacizumab was associated with a 3.5 times increased risk of FAEs in patients receiving taxanes or platinum agents, but was not associated with increased risk of FAEs when used in conjunction with other agents. Healthcare practitioners should monitor the patients closely to identify and treat serious adverse effects.

*(JAMA, Feb 2, 2011)*

### First-Line Erbitux in Lung Cancer

Researchers did a subgroup analysis of patients in the randomized Phase III First-Line Erbitux in Lung Cancer (FLEX) study, which enrolled patients with advanced non-small lung cancer (NSCLC) whose tumors expressed epidermal growth factor receptor. Landmark analysis assessed if the development of acne like rash in the first 21 days of treatment (first-cycle rash) was associated with clinical output. Acne like rash is the main cetuximab-related side effect. Results showed that first-cycle rash was associated with a better outcome in patients with advanced NSCLC who received cisplatin and vinorelbine plus cetuximab (erbitux) as a first-line treatment. They had significantly prolonged overall survival (OS) compared with patients in the same treatment group without first-cycle rash (median 15.0 months vs 8.8 months). Corresponding significant associations were also noted for progression-free survival. The significant OS benefit for patients with first-cycle rash versus

without first-cycle rash was seen in all histology subgroups. Thus, according to the subgroup analysis of data from this study, first cycle rash might be a surrogate clinical marker that could be used to tailor cetuximab treatment for advanced NSCLC to those patients who would be most likely to derive a significant benefit.

*(The Lancet Oncology, Jan 2011)*

### Induction Chemotherapy in Head & Neck Cancer

The long-term results of the TAX 324 randomized Phase III trial confirmed that adding a third drug (docetaxel) to a standard two-drug (cisplatin and fluorouracil) initial chemotherapy regimen significantly improves the long-term survival of patients with locally advanced squamous cell cancer of the head and neck. 501 patients were recruited from 55 centers across the USA, Canada, Argentina and Europe. Initial results (minimum follow-up 2 years) showed that induction chemotherapy with docetaxel, cisplatin and fluorouracil (TPF) significantly improved survival compared with PF. Over 6 years, the survival advantage was sustained and the addition of docetaxel reduced the risk of death by 26%. Overall survival was significantly better in the TPF group (70.6 months) than in the PF group (34.8 months). Additionally, progression-free survival was significantly longer for patients receiving the TPF than those on PF. The researchers concluded that patients who are candidates for induction chemotherapy should be treated with TPF.

*(Medical News Today, Jan 12, 2011)*

### Metastatic Breast Cancer

Docetaxel-trastuzumab (TH) is effective therapy for HER2 amplified metastatic breast cancer (MBC). Preclinical findings of synergy between docetaxel, carboplatin and trastuzumab (TCH) prompted multicenter Phase III randomized trial comparing TCH with TH as first-line chemotherapy for patients with HER2 amplified MBC (BCIRG 007 study). TH (trastuzumab plus docetaxel 100 mg/m<sup>2</sup>) and TCH (trastuzumab plus carboplatin at area under the serum concentration-time curve 6 and docetaxel 75 mg/m<sup>2</sup>) demonstrated efficacy with acceptable toxicity. There was no significant difference between TH and TCH in terms of the primary end-point, time to progression, response rate or overall survival. Adding carboplatin did not enhance TH antitumor activity.

*(JCO, Jan 10, 2010)*

## WATCH-OUT

### Antigen Express AE37 Cancer Vaccine

Genex Biotechnology Corporation, together with its wholly-owned immunotherapeutic vaccines subsidiary, Antigen Express, Inc, announced on February 3, 2011 that Antigen Express has received a Notice of Allowance from the United States Patent Office relating to an application making augmentative pharmaceutical composition claims for the Antigen Express AE37 immunotherapeutic cancer vaccine. This allowance strengthens independent composition of matter claims directed to the AE37 peptide. AE37 is currently under a randomized and controlled Phase II efficacy study in patients treated for breast cancer who are at high risk of recurrence. Favorable results from this study have been reported previously. This immunotherapeutic vaccine also has been tested in a Phase I study in patients with prostate cancer, which confirmed the safety and immunogenicity observed in the prior breast cancer study. In addition to breast and prostate cancer, many other types of cancer, such as lung, colon, stomach and bladder, also express the HER2 protein, which is the target for an AE37 stimulated immune response.

*(Genex Biotechnology Corporation, Feb 4, 2011)*

### Detection of Colon Cancer Marker

The fecal occult blood test is used extensively as a standard method for mass screening of colon cancer. It has low sensitivity and specificity (the sensitivity:30 to 90%, the specificity:70 to 98%). The present invention entitled "Method of Detecting Colon Cancer Marker" having Patent No US 2010323367, has been assigned to Olympus Corp (JP) on December 23, 2010. It is intended to provide a non-invasive and convenient method of detecting a tumor marker for diagnosing colon cancer which is superior in sensitivity and specificity to the existing fecal occult blood test. The collected biological sample (feces) is frozen using liquid nitrogen in some cases. The sample is homogenized in the presence of guanidine thiocyanate to extract RNA from the suspension. The extracted RNA is subjected to reverse transcription which gives cDNA. cDNA is amplified and then detected. This method is characterized by involving no procedure of separating cell components from the biological sample.

*(European Patent Office, Feb 7, 2011)*

### Endoscopic Mucosal Resection

Various endoscopic techniques for removing tissue from the walls of the gastrointestinal tract, are associated with difficulties of removing the entire suspect region and the risk of penetrating the muscularis during cutting. Ethicon Endo-Surgery, Inc has been assigned the US patent (No 7,86,228) entitled "Apparatus and Method for Performing an Endoscopic Mucosal Resection" on January 11, 2011. The present application relates to medical devices and methods for performing resection procedures within the gastrointestinal and esophageal passages of the human body. A surgical device including an elongated shaft having a distal end and a proximal end, an arm pivotally connected to the distal end and moveable through a dissection plane, and a cutting element disposed on the arm and adapted to move from an un-deployed configuration to a deployed configuration, wherein the cutting element is generally aligned with the dissection plane when in the un-deployed configuration and at least partially transverse with respect to the dissection plane when in the deployed configuration.

*(USPTO, Feb 1, 2011)*

### MRI Biopsy Device

The United States Patent and Trademark Office has assigned patent No 7,862,517 entitled "MRI Biopsy Device" to Devicor Medical Products, Inc. (Cincinnati, OH) on January 4, 2011. The invention relates to a method of imaging assisted tissue sampling and to an improved method for positioning a biopsy probe with respect to a magnetic resonance imaging (MRI) breast coil for acquiring subcutaneous biopsies and for removing lesions. A localization mechanism, or fixture, is used in conjunction with a breast coil for breast compression and for guiding a core biopsy instrument during prone biopsy procedures in both open and closed MRI machines. The localization fixture includes a three-dimensional Cartesian positionable guide for supporting and orienting an MRI-compatible biopsy instrument, and in particular a sleeve, to a biopsy site of suspicious tissues or lesions. A depth stop enhances accurate insertion, and prevents over-insertion or inadvertent retraction of the sleeve. The sleeve receives a probe of the MRI-compatible biopsy instrument and may contain various features to enhance its imagability, to enhance vacuum and pressure assist therethrough, and marker deployment etc.

*(esp@cenet.com, Feb 7, 2011)*

## GLOBE SCAN

### Cancer in Africa

Cancer in Africa is an emerging public health problem. According to IARC, about 681,000 new cancer cases and 512,400 cancer deaths occurred in 2008 in Africa. These numbers are projected to nearly double by 2030 due to the aging and growth of the population, with the potential to be even higher due to the adoption of behaviors and lifestyles associated with economic development and urbanization, such as smoking, unhealthy diet, and physical inactivity. Despite this growing burden, cancer continues to receive low public health priority in Africa, largely because of limited resources and other pressing public health problems. Cancers related to infectious agents (cervix, liver, Kaposi sarcoma, urinary bladder) are among the dominant forms of cancer in Africa. A majority of cancers in Africa are thought to be diagnosed at advanced stage of the disease largely because of lack of screening and early detection services as well as limited awareness of the early signs and symptoms of cancers among the public and healthcare providers. Survival after a diagnosis of cancer is much poorer in Africa than in the developed world for most cancer types.

*(Africa: American Cancer Society, Feb 7, 2011)*

### Generic Cigarette Packs

Both the Belgian Foundation against Cancer and the Association of European Cancer Leagues have called for the introduction of plain packaging for tobacco products in the revision of the 2001 EU Tobacco Products Directive. Plain packaging includes the removal of all attractive promotional aspects of tobacco product packaging. Except for the brand name, all other trademarks, logos, colour schemes and graphics would be prohibited. The package itself would be required to be plain coloured and to display only information (such as health warnings) required by law. Six research projects conducted by EU countries have come to the same convincing conclusion that plain cigarette packs are less attractive than the current ones, reduce the promotional appeal of the packs and enhance the visibility of the health warnings. Plain packaging is very likely to influence the international behavior to prevent or stop smoking.

*(Belgium: UICC, Jan 12, 2011)*

### Radiotherapy Awareness

Radiotherapy is one of the key treatments for cancer. Radiation as a cancer therapy was pioneered by Marie Curie, who won Nobel Prize for her work on Radium in 1911, exactly 100 years ago. Results of the research involving more than 2000 UK adults have shown that radiotherapy treatment helps cure four in ten patients, more than conventional chemotherapy. Survey also indicated that fewer than one in ten people think that radiotherapy is a modern cancer treatment. The survey results are being released to launch 2011 as the Year of Radiotherapy as part of the UK's National Radiotherapy Awareness Initiative designed to help improve public understanding and increase awareness of the value of radiotherapy. Improving access to, and uptake of radiotherapy would contribute to saving lives. New, more targeted radiotherapy techniques, such as intensity modulated radiotherapy and image guided radiotherapy are transforming the lives of patients with cancer, increasing cure rates and reducing side effects. Recently, published national cancer strategy has recognized the role of radiotherapy and committed additional funding.

*(UK: Cancer Research UK, Jan 31, 2011)*

### Advanced Cancer Care

The American Society of Clinical Oncology (ASCO) has called upon the physicians, medical schools, insurers, and others to help improve quality of life for people with advanced cancer. In a new policy statement, ASCO has outlined essential elements of care for patients with advanced cancer and identifies barriers that currently prevent advanced cancer care planning conversations between physicians and patients. The statement enumerates critical steps to ensure that care is individualized to address each patient's needs, goals and preferences throughout the course of their illness. The key elements include that physicians should initiate candid discussions about prognosis with their patients soon after an advanced cancer diagnosis. Physicians must help their patients to fully understand the potential risks and benefits of available cancer treatments and quality of life considerations. In cases where active treatment is unlikely to extend survival, palliative care should be discussed as a concurrent or alternative therapy. Increasing opportunities for these patients to potentially benefit from clinical trials and to contribute to improving cancer care should be a high priority.

*(USA: ASCO, Jan 25, 2011)*

**IN FOCUS**

**QUALITY OF LIFE ISSUES IN ONCOLOGY**

**Introduction**

Traditionally, the outcomes in cancer treatment were measured in terms of overall survival, disease-free survival and/or tumor response. With increasing implementation and success of multi-modality treatment, cancer has become a chronic disease more than a fatal one. The number of long-term survivors has increased. In patients cured of their disease, long-term sequelae of treatment may result in physical and/or emotional impairment. In incurable cancers, the aim of treatment is palliation of symptoms. In conventional treatment evaluation, there is no mention of assessment of physical or emotional impairment compromising the routine life of long-term survivors and the clinical benefit seen in patients living with cancer. Hence, conventional end-points used for the evaluation of treatment need a change. Recent compelling evidence shows, that patients who feel better, live longer. In fact, if one identifies patients who are not doing well and intervene, one may hope to improve not only the patients' sense of well-being, but also the length of their lives. Thus, quality of life (QoL) has become an important issue.

**What is Quality of Life?**

Quality of life (QoL) is a multidimensional concept. The World Health Organization's definition of health, 'a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity', has a strong underpinning about the quality of life. In clinical practice, QoL refers to the functional effect of an illness and its treatment on a patient, from the patient's point of view. This appraisal takes into account the patient's satisfaction with the current level of functioning in comparison to what he or she perceives to be possible or ideal. As such, each patient sets his/her own expectation level and provides his/her own opinion as to what level of dysfunction is acceptable or tolerable.

The assessment of QoL, as used in oncology, is the level of performance in 6 major domains of life:

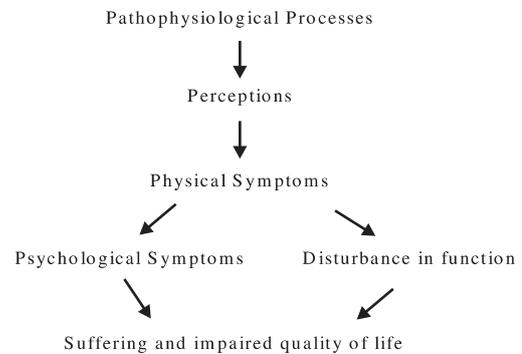
1. Physical – disease symptoms and treatment side effects
2. Functional – ability to perform usual activities
3. Psychological – mood, sense of well-being

4. Social – family, friends, leisure
5. Sexual – desire, performance
6. Work – usual level of activity as compared to the normal level for that individual.

Each of these can be measured by objective assessments of functioning and subjective perceptions of health.

**Why Assess Quality of Life in Oncology Practice?**

1. To identify, describe and compare cancer treatment effects and side-effects on patients receiving different treatment modalities/regimen.
2. To assess patient's QoL outcomes, identify rehabilitation needs and focus efforts to improve outcomes.
3. As a prognostic variable to assess whether QoL scores predict response to treatment modalities.
4. As a screening tool with multidimensional QoL to alert healthcare providers to morbidities that may go undetected (unexpected physical or emotional difficulty).
5. As an alternate end-point in treatment evaluation, given that increasing survival is the aim. When treatment outcomes are expected to be equal in comparable treatments, QoL issues determine the selection of a particular treatment.



A full assessment of the outcomes of cancer treatment involves a consideration of its impact not only on length of life, but also quality of life.

**How is Quality of Life Measured?**

Karnofsky and Burchenal in 1949 stressed that in addition to survival, subjective improvement was equally important to the evaluation of patients' responses to treatment. In 1984, US FDA demanded that efficacy of the new anti-cancer agents be demonstrated by improvement in survival or evidence of enhanced quality of life. It is particularly important to consider QoL outcomes when treatment is given with palliative intent or when toxic therapy is likely to yield only modest survival benefit. Broadly, the QoL issues are different in patients

under active treatment, during palliative care, for survivors and for healthy individuals who are at a known high risk.

### Which Instrument?

There are no 'gold standards' to assess QoL, but several scales are available to monitor function and effects of treatment. The choice of a measure depends on the QoL question being asked, the population being studied and the group to which it is to be compared.

Calman described QoL in inverse relation to the size of the gap between an individual's expectations and the real situation; the smaller the gap the better the quality of life. In a palliative setting, one has to keep this in mind, as the person's expectations are often adjusted as acceptance of functional limitations, secondary to disease progression, particularly in elderly patients.

1. Functional Living Index - Cancer (FLIC): Initially, the most widely used assessment, it is a 22-item scale with physical well-being and emotional sub-scales.

2. The Medical Outcomes Studies SF-36 is one of the best developed and validated general health status measures. It is a 36-item questionnaire that assesses patient health related QoL in eight dimensions or domains: physical functioning, limitations of role functioning from physical limitations, bodily pain, general perception of health, vitality, role limitations from emotional problems, social functioning, and mental health.

3. Cancer Rehabilitation Evaluation System (CARES), a 139-item scale across 6 QoL domains, captures content on disruption of daily activity due to disease and treatment.

4. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ30) is a modular QoL survey that consists of a core cancer survey and modular site-specific surveys that supplement the main instrument. The scales have a core of questions that are applicable to all patients with cancer and specific modules for certain disease sites (e.g. breast, prostate, and lung cancer). The EORTC QLQ-30 core questionnaire consists of six multi-item function scales (physical functioning, role function, social function, emotional function, cognitive function, and overall QoL), three symptom scales, and six single items.

5. Functional Assessment of Cancer Therapy (FACT), which adds an aspect of patient assessment regarding the difference between prior and present functions, is a general multidimensional QoL instrument for cancer patients. It is divided into domains for physical well-being, social and family well-being, and relationship with doctor, emotional well-being, and functional well-being.

In a palliative setting, specific measures for assessing symptom levels (including pain), psychological morbidity, and functional dependency scales would be more appropriate towards measuring the overall QoL. Additional scales, not developed specifically for cancer but widely used, are Psychological Adjustment to Illness Scale (PAIS) and Sickness Impact Profile (SIP).

Traditionally, these assessments have been in the form of interviews or forms to be filled during clinical visits. However, the use of trained telephone interviewers in some trials has been found to be more effective, being away from the hectic clinical setting.

Over the past 30 years, the field of QoL assessment has become sophisticated and methodologically rigorous. QoL instruments have made important contributions to therapeutic clinical studies, particularly concerning symptomatic treatments, where the clinical benefit ratio has shown improvement in weight, analgesic consumption and daily activities that may not be aptly reflected in the response evaluation measurements. The particular match, in terms of its sensitivity, specificity and interpretability between a study and its QoL instrument will all ultimately depend on the conceptual approach taken to measure QoL. Validated, translated questionnaires are available for use. The challenges posed by socio-economic and cultural differences in our population, the practicality of administration, make it necessary to develop indigenous tools and techniques for accurate assessment. Using the knowledge gained through QoLs to introduce timely measures for improving outcomes is another challenge in our settings.

### Conclusion

Quality of life is an important and essential measure of evaluating treatment outcomes. It is a patient's perspective on the impact of cancer and/or its treatment on his/her life. Its accurate assessment is capable of providing insight into the meaning of the disease and its treatment for the patient. Many instruments are available for the evaluation of QoL. Indigenous tools will further improve the accurate assessment of our population. Above all, QoLs can be helpful in guiding therapy, particularly effective and appropriate psycho-social interventions, which lead to favourable outcomes, not only in the quality but also the quantity of life.

*(Dr Rashmi Shirali, Physician, Investigator- Clinical Research; Dr D C Doval, Chief, Dept of Medical Oncology & Director Research)*



10<sup>th</sup> Annual International Conference of the  
Rajiv Gandhi Cancer Institute & Research Centre, Delhi, India  
February 4<sup>th</sup>-6<sup>th</sup>, 2011, India Habitat Centre, New Delhi



Rajiv Gandhi Cancer Institute and Research Centre (RGCI&RC), Delhi organized its 10<sup>th</sup> Annual International Conference "RGCON-2011" from 4<sup>th</sup> to 6<sup>th</sup> February 2011. The theme of the conference was "*Malignancies in Childhood*". The aim of conference was to provide the latest updates on various aspects of childhood cancer, including hematological malignancies, solid tumors, pain and palliation and late effects.

**The scientific program included:**

1. CME on "Molecular Biology and Cancer: Recent Trends"
2. Workshop on "Flowcytometry in Acute Leukemia and Detection of Minimal Residual Disease"
3. Nurses Workshop
4. Survivors Workshop
5. State-of-the-art lectures and symposia on ALL, AML, Transplantation, NHL, HL, Brain Tumors, Neuroblastoma, Bone and Soft Tissue Sarcomas
6. Presentations by young doctors to panel experts on practical problems in pediatric oncology clinical practice
7. Abstract papers

**Inauguration**

Chief Guest Dr Syeda Hameed, Member, Planning Commission, Government of India inaugurated the conference. Other guests included Dr. Lalji Singh, Padamshree Bhatnagar Fellow CSIR, Former Director, Centre for Cellular & Molecular Biology, Hyderabad who graced the inaugural ceremony. In the inaugural address, Dr Hameed informed that in the 12<sup>th</sup> Five Year Plan, one of the agenda is to take the treatment facilities to small towns and cancer treatment was one of them. Prioritizing health needs of women and children was her focus. Dr Lalji Singh stated that India is one of the largest human biodiversity pools in the world. He highlighted the genetic diversity in Indian populations and its implications in health and disease.

RGCON-2011 souvenir was released on this occasion. Three prestigious awards were given at the inaugural function. "Dr PS Raman Memorial Prize" for

the best publication of the Institute in the year 2010 was presented to Dr Akshay Tiwari, Associate Consultant, Dept of Surgical Oncology, RGCI&RC. Dr Sandeep Jain, Clinical Assistant, Pediatric Oncology was conferred with the "Young Doctor's Award". Dr DC Doval, Director Medical Oncology and Research, was bestowed with the award for "Excellence in Clinical Research".



(Dr A K Dewan, Medical Director, Shri Rakesh Chopra, Chairman and Dr Gauri Kapoor, Sr Consultant & Organizing Secretary, RGCI&RC; Dr Syeda Hameed, Member Planning Commission, Govt of India; Dr Lalji Singh, Padmashree Bhatnagar Fellow CSIR & Former Director CCMB Hyderabad; Shri D S Negi, CEO, RGCI&RC)

**Scientific Sessions**

Scientific program was crafted to include all childhood cancers touching on the basics, practical approach and recent advances. With galaxy of experts and delegates from India and abroad, RGCON-2011 provided a great opportunity in sharing and deliberating the latest advances in the field of Pediatric Oncology that would ultimately benefit the community of children with cancer.

Pediatric patients have heterogeneous group of malignancies and require multispeciality management. Keeping in mind the interest of different specialities, three parallel sessions were also organized simultaneously which included hematopathology, leukemia-lymphoma, and solid tumors. The young doctors interested in the field of pediatric oncology presented their work in the form of clinical cases, abstracts and oral presentation. Their work was critically reviewed by experts in the field, both from India and abroad.



(Dr Shripad Banavali, Tata Memorial Hospital, Mumbai; Dr SH Advani, Raheja Hospital, Mumbai; Dr Renu Saxena, AIIMS, Delhi; Dr VP Choudhary, Delhi; Dr Dario Campana, St Jude Children Research Hospital, USA)

### **CME on “Molecular Biology and Cancer: Recent Trends”**

Keynote address by Dr Lalji Singh was delivered to a rapt audience of young scientists. He discussed the genetic biodiversity of the human population. The other eminent speakers included Dr BC Das, Director, Dr BR Ambedkar Centre for Biomedical Research, Delhi, and specialists in the field from AIIMS, Delhi, and Shreis Scalene Sciences LLC (USA) & SSS (Canada) Inc. The CME received such an overwhelming response from delegates and faculty who participated actively that extra chairs had to be placed in the hall. We hope this event will encourage more youngsters to take up research in this field and unravel the mysteries of oncogenesis.

### **Workshop on “Flowcytometry in Acute Leukemia and Detection of Minimal Residual Disease”**

World experts Dr Dario Campana and Elaine Coustan-Smith from St Jude Research Hospital, USA’s top children’s cancer hospital, actively participated in conducting a 3-day state-of-the-art hands-on workshop on detection of minimal residual disease (MRD) in leukemia. The workshop participants included national experts from AIIMS, Delhi; TMH, Mumbai; R & R, Delhi; PGIMER, Chandigarh; CMC, Vellore; regional medical colleges, from Chennai, Manipal, Bangalore, Nepal as well as experts from the private sector.

Although the workshop was to be limited for 40 participants, the organizers were forced to allow over 60 registrations in view of its high calibre and popularity. This was only the second time such a workshop was organized in India. The deliberations were of such a high

standard that the interest level generated, led to packed halls on all the 3 days. Every one enjoyed and congratulated us for perfect time management throughout which in the language of flowcytometry is called – *tight gating!*

### **Nurses Workshop**

The workshop on On-Line Care and Chemotherapy basics was organized with the primary aim of updating the nurses about the care and maintenance of central lines and chemotherapy side effects and safety in drug delivery. The workshop was well attended and helped solve the common problems which are encountered in day to day pediatric oncology service.

### **Survivors Workshop**

Cankids and Ugam survivors of childhood cancer, from Delhi, Mumbai and neighbouring places were involved in a very interesting and interactive half-a-day workshop on survivorship issues. They also enacted street plays to highlight issues like ‘*Childhood cancer is curable*’.



(Engrossed Faculty and Delegates)

### **Conclusion**

RGCON-2011 was a unique opportunity for the Indian and international peers to open black boxes and exchange knowledge on best practices in childhood cancer. The conference was up to the expectations in terms of both scientific content and the hospitality. Everyone found the meeting useful and was able to take away new ideas and pearls of wisdom, which would help improve care of children with cancer.

(Dr Sandeep Jain, Clinical Assistant; Dr Himesh Gupta, Consultant, Pediatric Onco-Surgeon; Dr Gauri Kapoor, Sr Consultant, Dept of Pediatric Hematology & Oncology)



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2. Willis F et al, Expert Opin. Biol. Ther. 2002 Dec;2(8):985-92. 3. Liu Z, Appl. Health Econ. Health Policy. 2009;7(3):193-205.

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