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NewsLetter

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EDITORIAL

WATER POLLUTION – A PUBLIC HEALTH PROBLEM!

Any and all chemicals generated by human activity can and will find their way into water supplies. The types and quantities for carcinogens present in drinking water at the point of consumption will differ depending on whether they result from contamination of the source water; arise as a consequence of treatment processes or enter the way the water is conveyed to the user. Contaminated source water contains arsenic, asbestos, radon, agricultural chemicals and hazardous waste. Of these the strongest evidence for a cancer risk involves arsenic, which is linked to cancer of liver, lung, bladder and kidney. The use of chlorine for water treatment to reduce the risk of infectious diseases may account for a substantial portion of the cancer risk associated with drinking water. The byproducts of chlorination are associated with increased risk of bladder and rectal cancer. Research is needed to identify risks posed by contaminants from drinking water distribution pipes, joints, fixtures and microbial agents. According to a 2012 study **"finger print of Arsenic contaminated water in India – A review"**, arsenic contamination has been reported widely across northern states like Punjab, Haryana, Himachal Pradesh and UP. Ground water arsenic contamination has also been identified in lower Gangetic plains of West Bengal, Bangladesh and Terai regions of Nepal. Investigation by Central Ground Water Board has revealed that Arsenic contamination is affecting the states of Bihar, Assam and Chhattisgarh. Heavy metals from industrial waste dumped into water system and nitrates from excessive use of fertilizers are main source of contamination of drinking water. Punjab practices intensive agriculture with liberal use of pesticides. The state's use of chemicals is one of the highest in the country and residues have been found in the food as well. Farmers believe that higher the pesticides use, the greater is the yield. As fertilizers are heavily subsidized, the result is their excessive use of pesticides.

As Ganga river travels from the Himalyas into the Indo- Gangetic plains before emptying into Bay of Bengal, the Ganga is injected with a deadly cocktail of industrial pollutants and heavy metals. The river passes through 5 states crossing 26% the country land and supporting 43% of its population and all of them are helping pollute it further rather than clean it up. In July 2013, a report by Central Pollution Control Board (CPCB) made an inventory of 764 grossly polluting industries discharging waste water into mainstream of Ganga. The CPCB team found that industries consumed 1123 Million lit of water and discharged 500 million lit of effluent every day. Among the industrial units the tannery sector dominates while for waste water discharge the pulp and paper sector dominates followed by chemical and sugar sector. Ninety Percent of these industries operate in UP stretch of river.

Study in BHU noted that Ganga and Yamuna are already on the verge of a mega environmental disaster due to pollutant discharge at various locations such as Delhi, Mathura, Agra, Kanpur, Allahabad, Varanasi, Patna & Kolkata. These cities house various small scale industries which produce leather, paint, paper, pulp and batteries etc. In India about 80% of rural population and 50% of urban population uses ground water for domestic purposes. Water quality issues like Arsenic, Salinity, nitrates, fluorides and heavy metals in water have been reported from various parts of country. As many as 96 districts in 12 states have been affected by high Arsenic contamination in ground water. Over one lakh deaths are attributable to arsenic in water. 1.47 crore People in India face serious health hazards due to presence of arsenic in ground water.

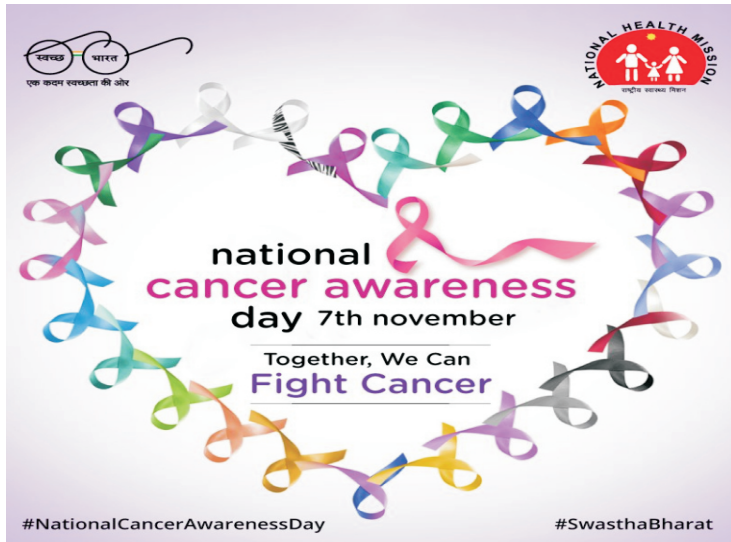
Secondly Ground water sources are being over exploited due to population explosion. In NCR Delhi, seven out of nine districts are categorized as over exploited with respect to dynamic ground water resources. In Delhi, aquifers in North, west and South west districts along Najafgarh drain contain lead. The southwest dist has cadmium and northwest, south and East Delhi has chromium making water toxic for human health.

According to water experts, unchecked industrialization has polluted two major water bodies – the Hindon and Yamuna rivers. Tonnes of sewage and industrial water from Delhi and Ghaziabad contaminate these water bodies. Secondly indiscriminate exploitation of floodplain water combined with relentless construction activity and sand mining have allowed the ingress of polluted water from these rivers to enter into plain aquifer. Under water reserves must not be exploited.

The highest risk comes from water systems that rely on ground water and supply mostly smaller communities. We need to prioritize source water protection and make sure that contaminants don't get into drinking water supplies to begin with.Let us protect our rivers – Prevent them from becoming toxic drains. Sewage treatment plants could be installed and effluents treated before drainage into the rivers. Stop indiscriminate exploitation of flood plain waters.

Let us prevent this public health tragedy – Water pollution!

Dr. A. K. Dewan
Director - Surgical Oncology



ADVANCES IN CHILDHOOD CANCER

INTRODUCTION

Every four of five kids with cancer are cured with the availability of 'multimodality' ie, surgery, chemotherapy and radiation and 'multidisciplinary' (nutrition, palliative care, physiotherapy, psychology etc in addition to oncology services) treatment.

With better understanding of ***cancer biology*** and advances in ***oncogenetics***, multiple molecular techniques have evolved to hunt for diagnostic and therapeutic targets, in childhood cancer.

Therapeutic advances have not just been limited to newer chemotherapy drugs, but we have come a long way to the use of '***precision medicine'*** which is largely based on matching the patient's tumor mutations with the appropriate targeted therapy. In the pediatric population, precision oncology is an area of highly active research, with efforts focused on fishing for drugable target by means of immunotherapy or targeted therapy. These were initially reserved for patients who are not cured with standard treatment and are gradually coming into frontline treatment strategies.

MOLECULAR DIAGNOSTICS: CLINICAL APPLICATION

Cancer Diagnosis

Mutation analysis is now routinely utilized to aid the diagnosis of various childhood cancers (Table 1). It also helps in characterizing the tumor, for example: translocation involving the FOXO1 gene is characteristic of alveolar subtype of rhabdomyosarcoma.

Some tumor or tissue-specific mutations and expression markers can be efficiently utilized for the diagnosis of cancers of unknown primary origin (CUPs). Systematic cataloging of tumor molecular portraits is likely to uncover a multitude of novel medically relevant DNA and RNA-based markers.

Specialized Molecular Techniques: Fluorescence in situ hybridization (FISH) and Polymerase chain reaction (PCR)

These tests are now an indispensable tool for confirmation of diagnosis and monitoring of disease in various childhood cancers.

These are valuable for detection of various mutations or translocations which can be exploited for planning therapeutic options in various cancers (figure 1).

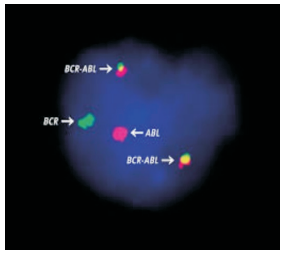


Figure 1:
15 year old male child diagnosed to have acute lymphoblastic leukemia . Bone marrow sample sent for FISH analysis revealed Bcr-abl translocation. Imatinib : tyrosine kinase inhibitor which targets this fusion transcript when added to standard chemotherapy significantly improves cure rates.

Liquid Biopsy

Tumors almost always shed their fragments (single cells or their clusters, DNA, RNA, proteins) into various body fluids. So-called liquid biopsy, i.e., the analysis of circulating DNA or some other tumor-derived molecules, holds a great promise for non-invasive monitoring of cancer disease, analysis of drug-sensitizing mutations and early cancer detection.

Molecular Sequencing: Next Generation Sequencing

NGS is a fast technology that allows for massively parallel sequencing of genomic fragments generating thousands to millions of short “reads” in a single run. It can detect point mutations including single nucleotide polymorphisms as well as small numerical aberrations (generally, less than 20–30 base pairs) coupled with powerful computational resources and analyze the data.

The progressive decrease in the cost of sequencing and the increase in the number of genes tested in a typical sequencing panel (from 50 to over 400 genes) has allowed for the high yield extraction of data and presented enormous opportunities to study rare and difficult to treat neoplasms .

Other advantages of NGS are that it can be performed from a low amount of input DNA, which is beneficial when small needle biopsies are obtained, and that it can be performed on DNA extracted from formalin-fixed, paraffin-embedded tissue.

STAGING AND RISK STRATIFICATION

Risk adapted treatment has given us an advantage of reducing intensity of treatment in low risk disease, and at the same time increasing the intensity in high risk disease. This has led to reducing both short and long-term treatment-related complications which is as important as cure, given the majority of childhood cancer patients will become long-term survivors. PET (positron emission tomography) is an exciting new imaging modality that is being increasingly used in oncology for staging and risk stratification.

PET scan

It is a nuclear scan used to examine the whole body at a single glance with the principle of increased glucose uptake at the site of increased metabolic activity (tumor site). These areas of disease will show up as bright spots on the PET scan (Figure 3)

This has simplified and objectified staging workup for many tumors.

PET scan has replaced the cumbersome method of staging, where separate CT scans of chest, abdomen, was required along with bone scans to stage a disease like Ewing sarcoma and rhabdomyosarcoma and can be done as a single imaging modality for staging.

Molecular techniques for risk stratification:

With the aid of molecular test (FISH/PCR/cytogenetic) various childhood cancers are characterized to be high or low risk , which has therapeutic and prognostic implication : (table 1)

Type of cancer	Molecular aberration	Risk stratification
Neuroblastoma	N-myc amplification	High risk
ALL	MLL rearrangement Bcr-abl translocation	High risk

AML	Monosomy 7	High risk

THERAPEUTIC ADVANCES

Immunotherapy:

Also called as biologic therapy, is a type of treatment that helps a person's own immune system to fight cancer. It can stop or slow the growth of cancer cells. Rationale of immunotherapy is to target a tumor antigen which is expressed on all or most of tumor cells.

- **Non-specific immunotherapy**. These boost the immune system in a general way, helping it attack cancer cells.
- **Oncolytic virus therapy**. Some viruses (called oncolytic viruses) can be changed in a laboratory so they infect and kill cancer cells. They also can help alert the immune system to fight the cancer cells.
- **Cancer vaccines.** These vaccines don't prevent diseases, as the flu and chickenpox vaccines do. Instead, they work against cancer by increasing the immune system's response to cancer cells in the body.eg : HPV and HBV vaccine.
- **CAR T-cell therapy**. Doctors take some T-cells from a patient's blood and artificially modify them in a lab to produce special structures called chimeric antigen receptors (CARs) on their surface. When these CAR T cells are re-infused into the patient, the new receptors enable them to latch onto a specific antigen on the patient's tumor cells and kill them. It has got miraculous results in multiply relapsed or refractory ALL and is now being used in various other high risk/refractory solid tumors eg : Neuroblastoma, glioblastoma multiformis
- **Antibody-drug conjugates** (monoclonal antibodies). These man made antibodies (disease-fighting proteins) help the immune system work by trying to attach to specific targets (markers) found on cancer cells. Some monoclonal antibodies (eg : GD2 in neuroblastoma) mark cancer cells so that they will be better seen and then destroyed by the immune system.
- **Bi-specific T-cell engagers (BiTE).** These man made antibodies can link a T-cell to a tumor cell. When the two cells are linked, the T-cell kills the tumor cell. Eg : CD 20 antibody –blinaumumab for ALL.

Targeted therapy

Targeted cancer therapies block specific proteins or genes that help cancers grow and spread. Personalized selection of cancer drugs based on the presence of actionable mutations has become an integral part of cancer therapy. Molecular tests underlie the administration of EGFR, BRAF, ALK, ROS1, PARP inhibitors as well as the use of some other cytotoxic and targeted drugs.

Table 2: role of molecular analysis in diagnosis, risk stratification and monitoring of disease.

MOLECULAR TARGET	TYPE OF CANCER	CLINICAL/ THERAPEUTIC USE
t(8;21) , t(inv 16), t(15;17)	AML	Aid in diagnosis
Bcr-abl	CML	Aid in diagnosis
t(11;22)	Ewings sarcoma	Aid in diagnosis
n-myc amplification	Neuroblastoma	Risk stratify
Bcr-abl/ t(9;22), t(4;11)	ALL	Risk stratify
FOXO-1 mutation	RMS	Risk stratify
Bcr-abl	CML	Monitor disease
t(15;17)	APML	Monitor disease
ALK	Neuroblastoma	Therapeutic target
FLT-3	AML	Therapeutic target
Bcr-abl	CML	Therapeutic target
t(15;17)	APML	Therapeutic target

RESPONSE ASSESSMENT

MRD: Minimal residual disease

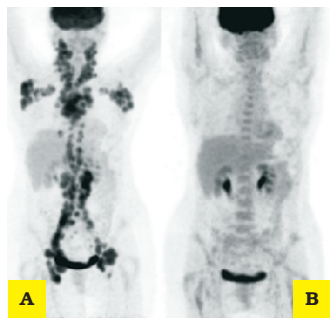
Minimal residual disease is the name given to small numbers of leukemic cells that remain in the person during treatment, or after treatment when the patient is in remission(all three cell lines within normal range, no palpable disease and no immature cells/<5% in bone marrow and peripheral smear) .

It assesses the depth of response to therapy and optimizing treatment as per response. Morphological assessments are still mandatory; however MRD surpasses it in terms of sensitivity, specificity and accuracy.

PET scan for response assessment:

Pet scan as discussed earlier, doesn't only aid in staging, rather is a powerful tool for intrim evaluation in various diseases like Hodgkin's lymphoma, non Hodgkin's lymphoma and metastatic solid tumors like Ewings sarcoma and RMS

Figure 2 : 20 year old female child diagnosed with Hodgkins lymphoma



A baseline F-18 FDG-PET/CT scan shows extensive disease, with widespread lymph node involvement above and below the diaphragm(A). The follow-up scan after completion of chemotherapy shows a complete response(B).

KEY MESSAGES:

- Phenomenal progress in all aspects of pediatric oncology.
- Increasing role of molecular techniques in diagnostics and tumor characterization.
- Use of newer imaging modalities in risk stratification and response evaluation.
- Emphasis on efforts to reduce the late effects of treatment.
- Evolving role of immunotherapy and targeted strategies.
- Globally unending efforts to ensure that" no child should die of cancer".

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ARM PORT TRAINING WORKSHOP

The Department of Surgical Oncology and Department of Intervention Radiology successfully organized Arm Port Training Workshop on Saturday, 31st August 2019 at RGCIRC, Rohini. We were honoured to have a visiting faculty, Dr. Sundeep J. Punamiya, Intervention Radiologist at Tan Tock Seng Hospital, Singapore with us. The one day program included interactive lectures in the morning followed by live case demonstrations of Arm Port insertion in the IR Suite of RGCIRC (Cath lab). It was attended by 4 external candidates and 4 internal candidates. The workshop was highly gratifying and we received an excellent feedback. This was the first time that a training workshop for insertion of Arm port was held in India.

CME – IMA MUZAFFARNAGAR

RGCIRC organized a CME in association with IMA Muzaffarnagar, UP on Wednesday, 9th October 2019 at IMA House, Muzaffarnagar, UP. Dr. Leena Dadhwal, Consultant – Surgical Oncology delivered a lecture on Recent Advances in Management of Breast Cancer and Dr. Mudit Agarwal, Sr. Consultant – Head & Neck Surgical Oncology spoke on Role of Robotic Surgery in Head & Neck Cancer Management. The CME was very well appreciated by the gathering.

CME - IMA JHANSI

RGCIRC organized a CME in association with IMA Jhansi, UP on Friday, 11th October 2019 at Hotel Sheela Shree Plaza, Jhansi, UP. Dr. A. K. Dewan, Director - Surgical Oncology delivered a lecture on What is Latest in Oncology and Dr. Sajjan Rajpurohit, Consultant - Medical Oncology spoke on Cancer Vaccines: Myths vs. Reality. The CME was very well appreciated by the medical audience.

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