

**PATRONS**

AVM H L Kapur  
Shri B L Joshi

**GOVERNING COUNCIL**

*Chairman:* Dr K V Swaminathan  
*Vice Chairman:* Smt Renu Karnad  
*Hony Secretary:* Smt Jyotsna Govil  
*Treasurer:* Shri O P Nayar  
*Principal Advisor:* Shri K K Mehta

**Members**

Shri Madan Agarwal  
Shri R N Bansal  
Smt Harmala Gupta  
Shri Rakesh Chopra  
Shri Pramod Maheshwari  
Shri R K Ahooja  
Dr Sunil Khetrapal  
Shri B Swarup  
Shri O P Gariyali  
Shri P V Jaishankar  
Representative of LG of Delhi

**RESEARCH ADVISORY COMMITTEE**

Dr K V Swaminathan  
Dr S P Tripathy  
Dr Ashok Mohan  
Dr R A Badwe  
Prof A B Dey  
Dr K Satyanarayana  
Dr Panna Choudhury  
Dr M Siddiqui  
Dr Prema Ramachandran  
Dr N K Grover  
Dr Tejinder Kataria  
Dr A K Vaid  
Dr G L Telang  
Representative of DGAFMS  
Representative of DGHS  
Director ICPO  
Dr A K Dewan  
Dr D C Doval

**RESEARCH & ANALYSIS TEAM**

**Editor:** Dr D C Doval  
*Director Research*

Ms Rupal Sinha *Research Officer*  
Mr Saud Azam *Research Officer*  
Mrs Swarnima Jaitley *Research Officer*  
Dr (Mrs) Harsh Sachdeva *Research Officer*

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

***From the Desk of Director Research***

Progress in Pediatric Oncology is one of the biggest success stories in oncology in the last millennium. The 10<sup>th</sup> Annual International Conference "RGCON-2011" being organized by the Institute from February 4<sup>th</sup> to 6<sup>th</sup> has its main theme as "Malignancies in Childhood". It would be a perfect forum to interact with the eminent international and national faculties.

In this issue, "Childhood Cancer Facts" gives a glimpse of prevalence and treatability of childhood cancer while the "Special Feature" profiles 'Childhood Cancers in India: Epidemiology, Challenges and Breakthroughs' and the fundamental steps in caring for these children. Substantial progress has been made in the field of stem cell transplantation. A special gratitude to Dr Vinod K Prasad, Duke University Medical Center, USA for contributing the "Guest Article" on 'Hematopoietic Stem Cell Transplantation: Survival Opportunity for Patients with Fatal Diseases'.

Flow cytometry is an indispensable tool for the diagnosis and monitoring of haematologic neoplasms. "Perspective" highlights "Value of Flow Cytometric Analysis in Pediatric Haematolymphoid Neoplasms" whereas "In Focus" gives an overview of 'Advances in Pediatric Cancer Treatment and Current Challenges'. The new avenues of research have been briefed under "Hope in Battle Against Childhood Cancers".

In general practice, cancer is relatively rare in children and is easily missed. Early diagnosis and prompt treatment improves prognosis. Keeping these in view, this special issue covers "Childhood Cancer: Tips for General Practitioners".

A special thanks to Eli Lilly Oncology Division for sponsoring this issue of Cancer News. We also gratefully acknowledge the contributions made by Clinicians, Scientists, DNB and FNB students of the Institute. Views and suggestions from readers are welcome.

*Dr D C Doval*

**CONTENTS**

- **Childhood Cancer Facts [3]**
- **Special Feature:** Childhood Cancers in India: Epidemiology, Challenges and Breakthroughs [4-6]
- **Guest Article:** Hematopoietic Stem Cell Transplantation: Survival Opportunity for Patients with Fatal Diseases [7-9]
- **Perspective:** Value of Flow Cytometric Analysis in Pediatric Haematolymphoid Neoplasms [10-11]
- **In Focus:** Advances in Pediatric Cancer Treatment and Current Challenges [12-14]
- **Hope in Battle Against Childhood Cancers [14]**
- **New Technologies:** A Big Leap for Neuroblastoma; Dexrazoxane for Cardioprotection; Endoscopic Procedure for Brain Tumor; Novel PEGylated DNA Topoisomerase 1 Inhibitor; Robotic Drug-Screening Technology [15-16]
- **Globe Scan:** Good Follow-Up Healthcare; To Step Up Childhood Cancer Fight [16]
- **Immunization in Children with Cancer [17]**
- **Childhood Cancer: Tips for General Practitioners [18-19]**

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

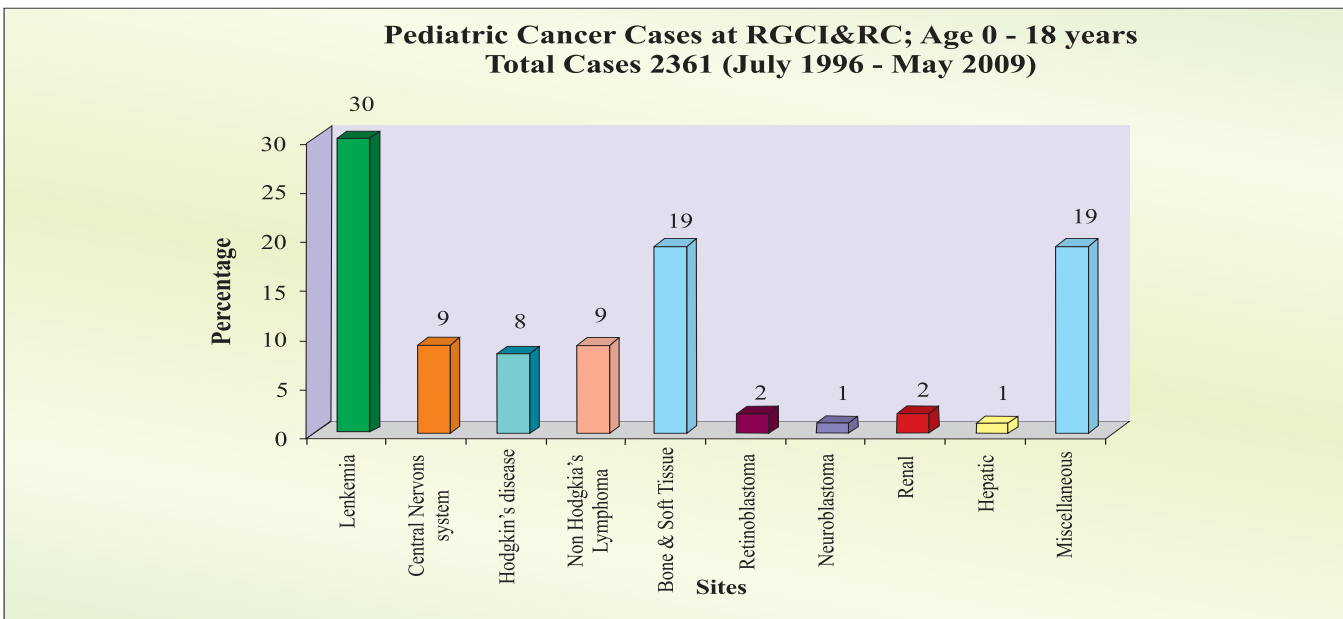
Printed at  
Sagar Printers &  
Publishers,  
1880 Udaichand Marg,  
Kotla Mubarakpur,  
New Delhi - 110 003

**CHILDHOOD CANCER FACTS**

- Cancer in children is highly curable.
- Progress in Pediatric Oncology is one of the biggest success stories in oncology in the last millennium. The 5-year survival for all pediatric cancers is now 75-80%. Despite having made steady progress in the last few decades; India is yet far behind the current international standards.
- Childhood cancer constitutes to less than 5% of the total cancer burden in India, with approximately 45,000 children diagnosed with the disease every year.
- In India, 1.6-4.8% of all cancer cases occur in children less than 15 years of age with variation by place of residence. Thirty-three percent of the population in India is less than 15 years of age.
- Reported incidence of childhood cancer in India in males (39-150 per million children/ year) is higher than in females (23-97 per million children/year) in all population based registries, except in North East India.
- Leukemia is the most common childhood cancer in India with relative proportion varying between 25 and 40%. Sixty to eighty-five percent of all leukemias reported are acute lymphoblastic leukemia (ALL).
- Families need information to be aware of symptoms, accept the illness and take the child for treatment without fear of recrimination, rather than relying on traditional healers.
- The majority of children with cancer require rounds of chemotherapy to treat their disease. Many

- require surgery and/or radiation to remove the tumor. For some, a bone marrow transplant is the only hope of survival.
- As more and more children are surviving cancer, it is increasingly important to address ongoing and emerging needs of children and their families in order to achieve complete and long term healing.
- During palliative end of life care, psychosocial support is more critical than ever, since nothing matters then except the child’s quality of life. At this time attending to the family’s support networks and acknowledging their emotional and spiritual needs are paramount.
- The outcome of pediatric cancer has gradually improved in the country over the last four decades. The outcome of hematological cancers in terms of long-term survival has greatly improved from 20% to 60% in ALL, from <70% to more than 90% in Hodgkin's disease, from 30% to 70% in non-Hodgkin’s lymphoma and from 10% to 40% in acute myeloblastic leukemia. Similarly, the outcome in solid tumors has also improved.
- It is hoped that according due consideration to the need of the vulnerable child with a life-threatening disease may contribute to an improved environment for all the children.
- Public understanding about the prevalence and treatability of childhood cancer in the developing world can bring pressure on governments to take action and on drug companies to control drug costs.

*(Reviewed by Dr Himesh Gupta, Consultant, Pediatric Onco-Surgeon; Dr Gauri Kapoor, Sr Consultant, Dept of Pediatric Hematology & Oncology)*



## SPECIAL FEATURE

### CHILDHOOD CANCERS IN INDIA: EPIDEMIOLOGY, CHALLENGES AND BREAKTHROUGHS

#### Introduction

Worldwide, the annual number of new cases of childhood cancer exceeds 200,000 and more than 80% of these are from the developing countries. There has been enormous progress in the treatment of childhood cancer in the developed world. Seven out of 10 children with cancer in the resource-rich countries are cured, with a five-year survival for certain cancers, for example, Hodgkin's disease and retinoblastoma, now being 95%.

In India, childhood cancer is not yet a major area of focus. The emphasis at present is on reduction in mortality of infants and under-fives, by promotion of breast feeding, rational antibiotic therapy for acute respiratory infections, oral rehydration for diarrhea and Universal Immunization Program.

Cancer care thus remains a challenge. In India, there is an urgent need to appreciate the fact that cancer in children is highly curable in expert hands. The fundamental steps in caring for these children are to estimate the current burden, understand and overcome the barriers, and develop strategies to detect early, refer and treat cancers with appropriate expertise.

#### Burden of Childhood Cancer

Cancer is generally regarded as a disease of the adults. In England, only 0.5% of all cancer cases occur in children less than 15 years of age. In India, however, this proportion is higher at 1.6-4.8% with variation by place of residence.

Despite there being a higher proportion of childhood cancer in India relative to the developed world, it has not been a priority in healthcare. This is because of its contribution to the overall childhood mortality. Excluding neonatal deaths, infectious and parasitic diseases are the most common cause of death in children in India.

Only 2% of all deaths in this age group are reported to be cancer-related deaths. This contrasts with data from England and Wales where injuries are the most common cause of overall death in children (21%) and cancer the most common cause of disease-related death (20%). However, with the economic growth and

improvement in healthcare in India, in the next decade, infectious disease-related deaths will be controlled. So, mortality due to cancer will become prominent in the near future.

#### Incidence of Childhood Cancer

**Overall Incidence:** The incidence of childhood cancer in most populations in the world ranges from 75 to 150 per million children per year. The reported incidence in urban India (Bangalore, Bhopal, Chennai, Delhi, Mumbai) is generally higher than from rural areas (Barshi and Ahmedabad district) and is comparable with the average world incidence. This may be due to under-ascertainment of cases and registration in rural areas, but this remains to be confirmed.

**Variation by Sex:** Most of the resource-rich countries have male to female ratio of 1.2:1. However, some cancers like retinoblastoma, Wilms tumor, osteosarcoma, and germ cell tumor actually show a slight female preponderance. The reported incidence of childhood cancer in India in males (39-150 per million children per year) is higher than in females (23-97 per million children per year) in all population based cancer registeries, except in North East India. Gender bias in seeking healthcare, including treatment of cancer, is one possible explanation. Arora R S et al reported 12-fold higher incidence of Hodgkin's disease in male children in Delhi, it needs to be further investigated.

#### Variation by Cancer Type

**Leukemia:** It is the most common childhood cancer in India with relative proportion varying between 25 and 40%. Sixty to eighty-five percent of all leukemias reported are acute lymphoblastic leukemia (ALL). Compared to the developed world, the biology of ALL appears different in India, with a higher proportion of T-Cell ALL (20-50% as compared to 10-20% in the developed world), hypodiploidy and translocations t(1;19), t(9;22), and t(4;11), all of which contribute to a poorer prognosis of this leukemia.

**Lymphomas:** In the developed world, central nervous system tumors are the second most common childhood cancer (22-25%) and lymphomas a distant third (10%). Not only is the proportion of lymphomas higher in India, but HD exceeds non-Hodgkin's lymphoma (NHL), a pattern opposite to that seen in the developed world. Besides differences in incidence, the pathobiology of these cancers is also different. Among NHL, the proportion of T-cell lymphoblastic lymphoma and diffuse

large B-cell lymphoma is much higher and the proportion of mature B-cell (Burkitt's and Burkitt-like) lymphoma much lower in India than that seen in the developed world. The high proportion of mixed cellularity in India is thought to be related to early childhood Epstein Barr virus exposure.

**Central Nervous System (CNS) Tumors:** In the larger urban areas of Bangalore, Chennai, Delhi, and Mumbai, the incidence rate is 10-20 per million children per year, which is half of that in the developed world. A relative paucity of neurodiagnostic and neurosurgical facilities could possibly explain the differences in incidence in India.

**Survival from Childhood Cancer**

The largest contributor to mortality from childhood cancer in Britain are CNS tumors, reflecting the relatively poor survival in this group, followed by leukemias and neuroblastomas. In contrast, in India, leukemia continues to be the largest contributor to cancer-related mortality in children, followed by lymphomas and CNS tumors, which have similar mortality rates. This pattern is a result of the relatively high incidence of lymphomas, low incidence of CNS tumors, and a lower survival of all cancers, including leukemias in India (see Table).

**Challenges in India**

With centralization of treatment and enrolment in clinical trials in the developed world, a five-year overall combined survival for all childhood cancers is now 75-80%. Similar outcomes have been achieved in India in those treated at tertiary institutes like Rajiv Gandhi Cancer Institute, New Delhi and Tata Memorial Hospital, Mumbai. However, unfortunately one cannot extrapolate these results to cover whole population where survival is disappointingly low and which may be related to an advanced stage at presentation and

suboptimal chemotherapy regimens used.

Multiple inter-related factors are responsible for the poorer outlook of childhood cancer in India:

- Limited financial resources
- Lack of awareness of symptoms
- Difficulty in accessing healthcare
- Poor referral system
- Paucity of good tertiary care centre
- Non recognition as a major child health problem

Thus, there is lack of initiation at multiple levels in healthcare in India which hamper curing the vast majority of our children with cancer as well as palliating the rest of avoidable pain and suffering.

Of late, twinning programs, which foster interactions between public hospitals in developing countries and established cancer treatment centers in developed countries, have been seen to reduce abandonment and improve survival. Similar strategies could be applied here.

Clinical trials started by the Indian Cooperative Oncology Network (ICON) and adoption of the MCP-841 protocol for ALL in major Indian centers have been steps in the right direction for improving childhood cancer outcome.

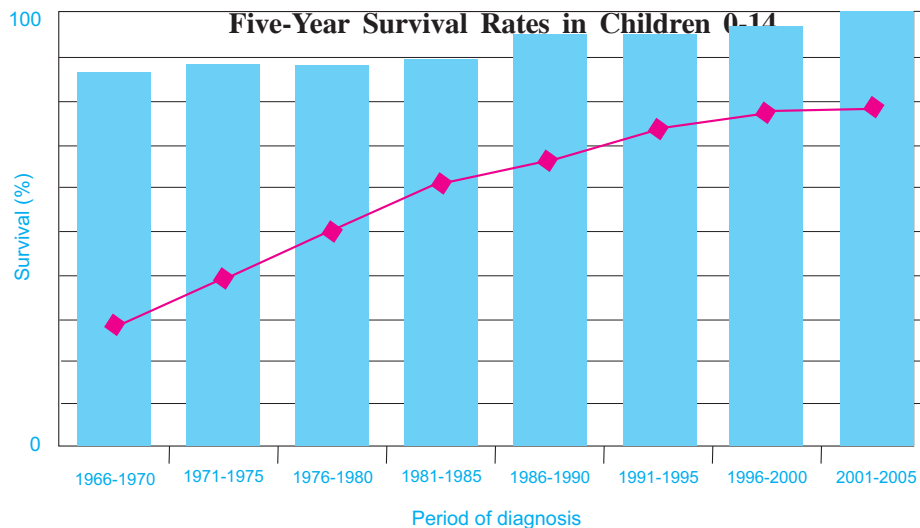
**Breakthroughs and Progress in India**

Though the progress has been slow, the urgent need to address this problem that plagues the future of the nation is gradually being realized. The breakthroughs so far have been as under:

- To improve physician experience, a successful national training program in practical pediatric oncology (NTP-PPO) has been initiated by Pediatric Hematology Oncology Chapter of Indian Academy of Pediatrics (IAP).

**Table : Five-year overall survival (expressed in percentage) of common childhood cancers in India, Europe, and USA**

Cancer type (categorized by the International Childhood Cancer Classification)	Population registry data		Single hospital	Population registry data	
	Bangalore	Chennai	Mumbai	Europe	USA
	1982 to 1987	1990 to 2001	Various periods	1993 to 1997	1996 to 2004
Leukemia		36		77	81
Lymphoid leukemia	35	39	60	82	86
Acute myeloid leukemia	10	30	58	52	57
Lymphomas		55		85	87
Hodgkin's disease	72	65	94	93	95
Non-Hodgkin's lymphomas	33	47	58	79	84
CNS tumors		27		67	71



*Survival Data from Developed World*

- Reputed institutes like Rajiv Gandhi Cancer Institute & Research Centre have started super specialty two years Fellowship training in pediatric hemato-oncology (FNB), which is accredited by the National Board program.
- There is formation of national oncology groups, such as Indian Cooperative Oncology Network (ICON), and Indian National Pediatric Oncology Group (InPOG). These collaborative efforts will go a long way in the shaping of holistic care and better future for children with cancer. They will also prove valuable to researchers, epidemiologists, administrators, support groups and all individuals engaged in effective treatment of childhood cancer in India.
- For sensitization to early diagnosis and prompt referral, the ICON has started a PromOTE-Pediatric Campaign.
- Establishment of online web-based India Pediatric Oncology Database (IndiaPOD).
- RGCI&RC is the pioneer super-specialty cancer centre in North India. The Institute has a state of the art pediatric hemato-oncology department for the past 14 years, comprising of highly skilled multidisciplinary team. It has world class facilities like a dedicated unit for allogeneic and autologous transplants, high dose chemotherapy (e.g. methotrexate in osteosarcoma and acute lymphoblastic leukemia) and limb salvage surgery.

Hopefully these efforts would start bearing fruits in the near future.

### **Future**

The fact that cancer in children is highly curable must be realized clearly by the government and policy

makers at the earliest. There should be incorporation of childhood cancer care in the Integrated Management of Neonatal and Childhood Illnesses (IMNCI) program. This would lead to early detection and referral, resulting in better prognosis. The IAP has created a InPOG. It will focus on developing cost effective and logistically feasible protocols for Indian children. International collaboration will contribute to this. The detection of cancer in children not only devastates the parents psychologically and socially, it also causes financial impoverishment of the whole family. So, these families must receive liberal financial support from the government and non-government organisations. Use of mass media to spread awareness among the general population should be encouraged.

### **Conclusion**

Public understanding about the prevalence and treatability of childhood cancer in the developing world can enjoin governments to take action and on drug companies to moderate drug costs. In an ideal world, children with cancer should have access to the best treatment and pain control and at the same time go to school and take part in normal life as far as possible. RGCI&RC would like to fulfil the dream of legendary Danny Thomas, the founder of St. Jude Children's Research Hospital, that "No child should die in the dawn of life". We must hope that feasible initiatives by the concerned to meet the need of the vulnerable child with a life-threatening disease would contribute to an improved environment for all children.

*(Dr Sajjan Singh, DNB Student; Dr Gauri Kapoor, Sr Consultant, Dept of Pediatric Hematology & Oncology)*

**GUEST ARTICLE**

**HEMATOPOIETIC STEM CELL TRANSPLANTATION: SURVIVAL OPPORTUNITY FOR PATIENTS WITH FATAL DISEASES**

**Hematopoietic stem cell transplantation (HSCT)** - an umbrella terminology that encompasses bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSCT) and umbilical cord blood transplantation (UCBT) – has been successful in the treatment of many life threatening diseases in children and adults. Advances in blood bank services, availability of better antibiotics, safer anti-fungal and anti-viral agents, as well as developments in DNA sequencing technologies to identify more suitable donors have led to incremental but significant improvements in the survival and overall outcomes following HSCT. Support from many departments in the hospital and use of highly trained and skilled staff, including nurses, are critical to developing a successful transplant unit and achieving high survival and low short- and long-term complications.

Every year 13,000-14,000 HSCT (17% in children) are reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) from centers worldwide. The therapeutic advantage of HSCT stems from the ability to give more intense treatment, the replacement of a defective marrow, and the anti-neoplastic effect mediated by the immune cells derived from the donor stem cells, a phenomenon known as the graft-versus-tumor or graft-versus-leukemia (GVL) effect. Allogeneic hematopoietic cells were first successfully transplanted in 1968 in three children with congenital immunodeficiency. These early successes were the result of preceding experience from animal studies, in particular those performed by E. Donald ‘Don’ Thomas who in 1990 was awarded the Nobel Prize for these pioneering studies that paved the road for clinical transplantation. Since then >200,000 transplants have been performed and countless lives have been saved worldwide. Currently, HSCT is indicated in the treatment of a large number of childhood and adult diseases (Table 1), including leukemia, lymphoma, and a variety of hematologic malignancies. There is increasing interest in the use of HSCT in non-malignant diseases, such as hemoglobinopathies, inborn errors of metabolism, and autoimmune diseases.

**Table 1: Partial List of Diseases that can be Treated by HSCT**

MALIGNANT	NON-MALIGNANT
<b>Leukemia/Pre-leukemia</b>	<b>Bone marrow failure syndromes</b>
Acute lymphoblastic leukemia	Severe aplastic anemia
Acute myeloid leukemia	Kostman’s syndrome
Chronic myeloid leukemia	Fanconi Anemia
Myelodysplastic syndromes	Other marrow failure syndromes
<b>Hodgkin’s and non-Hodgkin’s lymphoma</b>	<b>Genetic disorders</b>
	Krabbe disease
<b>Multiple Myeloma</b>	Hurler syndrome (and other mucopolysaccharidoses)
	Metachromatic leukodystrophy
<b>Solid Tumors</b>	Adrenoleukodystrophy
Neuroblastoma	Osteopetrosis
Malignant brain tumor	
Sarcoma	<b>Hemoglobinopathies</b>
Retinoblastoma	Sickle cell disease
Wilms’ tumor	Thalassemia
	<b>Immune deficiency</b>
	Chronic Granulomatous disease
	Severe combined immune deficiency
	Combined immune deficiency
	Familial Erythrophagocytic Lymphohistiocytosis
	Leukocyte adhesion defect
	Wiscott-Aldrich syndrome
	Other immune deficiencies
	<b>Autoimmune disease</b>

The HSCT can be **autologous** or **allogeneic**, depending on the donor source. In autologous transplantation, the patients serve as their own donor. These transplants are performed by collecting hematopoietic stem cells from the patient by leucopheresis or bone marrow harvest and then cryopreserving the cells. These cells are reinfused into the patient following high dose chemo- and/or radiation therapy to reconstitute the ablated marrow. The transplant-related mortality is lower primarily because of the absence of graft-versus-host disease (GVHD) and a more rapid immune recovery. However, immune-mediated anti tumor or graft-versus-leukemia effects, are absent, resulting in higher post-transplant relapse rates. There is also a concern about re-infusing cancer cells, which may potentially be contaminating the graft.

Allogeneic grafts have in the past been derived either from the bone marrow or granulocyte colony stimulating factor (GCSF)-mobilized peripheral blood from either related or unrelated donors. The patient and donor have to be matched for the determinants of alloreactivity to ascertain good outcome. The most useful factor for matching the donor-recipient pairs is the Human Leukocyte Antigen (HLA) gene complex, located on the short arm of the chromosome 6. The gene complex consists of many loci, each with two alleles; one inherited from the father and one from the mother. The loci most relevant in human transplantation are HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1. The HLA inheritance is governed by the Mendelian principles and thus there is approximately a 25% chance that two siblings will match each other. The overall chances of finding a suitable donor within a family are less than 35% in the United States. For the remaining children, either an unrelated adult donor or unrelated cord blood unit must be found. The extensive polymorphism of human HLA genes creates challenges for finding suitable donors. Preliminary search to identify donor can be requested by any physician. These searches are done by central computers from within approximately 16,000,000 volunteer unrelated donors listed in multiple registries and approximately 500,000 unrelated donor cord blood units preserved in various public cord blood banks.

In recent years, **umbilical cord blood**, a rich source of hematopoietic progenitors has emerged as a successful form of donor transplant for patients lacking a matched donor. The first umbilical cord blood transplant (UCBT) from a matched sibling was performed in Paris on a patient from North Carolina with Fanconi Anemia. The first unrelated UCBT in the world was performed at Duke University Medical Center in 1993. Since then more than 15,000 UCBT have been performed worldwide. Unrelated UCBT has advantages, including rapid availability of pre-prepared units and less stringent requirements for HLA matching, because of greater immune tolerance and lower incidence of GVHD. One disadvantage of UCBT is slower myelopoietic engraftment and immune reconstitution. However, unrelated UCBT provides greater access to transplant therapy for patients belonging to ethnic and racial minorities, those with rare HLA types, and those who do not have an acceptable match from an adult donor. UCBT is seen to

be particularly useful in the Indian context and it is hoped that more centers in India will develop the expertise in this field. Due to high fertility rates in India, there is a huge potential to collect umbilical cord blood and use it for HSCT. Each cord blood unit has a potential to save a life and it is tragic that thousands of placenta full of cord blood are discarded in India everyday as medical waste.

Prior to the transplant, the patient undergoes **conditioning** consisting of either chemotherapy drugs or a combination of chemotherapy and radiation. The pre-transplant ‘conditioning’, or ‘cytoreduction’, or ‘preparative regimen’, is an integral part of the transplant process and is used to destroy abnormal/malignant cells as well as to achieve immunosuppression and thus prevent the host from rejecting the donor stem cells. Variety of chemo and radiation combinations (Table 2) are in use and are selected on the basis of patient characteristics like diagnosis and organ function

**Table 2: Common Preparative Regimens and Indications**

Preparative Regimen	Common diseases
TBI / Cytoxan	ALL, AML, lymphoma, CML, MDS
TBI / Melphalan	AML
TBI / Thiotepa/Cytosan/ ATG	ALL, AML for TCD transplants
TBI / VP16	Acute and chronic leukemias
Fludarabine / Busulphan	Leukemia, Hodgkin disease & NHL
Cytosan / VP16/TBI	AML, MDS
Busulphan / Cytosan / ATG	Metabolic & genetic disorders for UCBT
Busulphan / Cytosan	AML, MDS
Cytosan / ATG	Severe aplastic anemia
BEAM / TEAM or Cytosan/ BCNU / VP16	Hodgkin’s disease and NHL
Reduced Intensity Regimens	Too old or sick to get regular transplants
Auto-transplants	Solid tumors

*(TBI, total body irradiation; VP16, etoposide; ATG, antithymocyte globulin; BEAM, BCNU/ carmustine, etoposide, cytarabine, melphalan; TEAM, same as BEAM except thiotepa instead of BCNU; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CML, chronic myeloid leukemia, MDS, myelodysplastic syndrome; Non-Hodgkin lymphoma; UCBT, umbilical cord blood transplant; TCD, T cell depleted)*

profile as well as graft characteristics. Radiation is usually given as total body irradiation (TBI) in multiple fractions over period of 4-5 days, usually totaling 1200 - 1550 cGy. Bone marrow is collected from the donor under anesthesia from the iliac crest while PBSC are collected by leucopheresis after the donor has received GCSF over the previous 4-5 days. On the other hand, cord blood cells are procured from public cord blood banks and thawed and usually washed prior to transplantation. Donor stem cells are infused intravenously, using central venous catheter and migrate through the bloodstream to home into the marrow spaces. Engraftment of the hematopoietic cells occurs over a variable period of 2-4 weeks until which time the recipient is severely immunocompromised and pancytopenic. During this period, the recipient is completely dependent upon supportive care consisting of blood product transfusions, total parenteral nutrition (TPN), and antibiotics.

**Post transplant periods** are early (0-100 days), and late (>100 days). Complications depend to an extent on the period. For example, infection, acute GVHD, and graft failure are frequent complications in the early period. Infections are very common and lead to considerable morbidity and mortality. GVHD results when donor derived T-cells present in or derived from the graft attack the patient as foreign causing multi-organ complications (see below). The clinical features are dependent on the time of GVHD in relation to the date of transplant. The incidence and severity of GVHD depend on a number of factors but typically increase in older patients, and with degree of HLA mismatch between the donor and the patient. Acute GVHD in the early period following HSCT can cause rash, diarrhea, hyperbilirubinemia. A systemic syndrome with fever and generalized capillary leak syndrome, including pulmonary edema, is called either as hyperacute GVHD or engraftment syndrome. In the late post transplant period (> 100 days), recurrent primary disease, chronic GVHD, avascular necrosis (AVN) and secondary malignancies become increasingly important. Chronic GVHD can manifest as various types of rash including scleroderma, mouth plaques, xerostomia, chronic diarrhea, malabsorption, gastrointestinal stricture, and sometimes autoimmune disease. Importantly, UCBT is associated with lower incidence and severity of acute and chronic GVHD when compared with bone marrow or peripheral blood stem cell transplant

**In conclusion,** advances in HSCT, including improved supportive care and better understanding of immunology, have led to an increasing survival and acceptance of HSCT as the standard of care for many diseases. However, the full potential of this revolutionary therapy can only be achieved if high quality transplant centers are developed across the world, especially in India, home to a sixth of humanity. *(Adapted from previous works by the author Dr Vinod K Prasad, MD, MRCP (London), Pediatric Bone Marrow Transplant Faculty, Duke University Medical Center, Durham, NC, USA)*

### CHILDHOOD CANCER SURVIVORS: QUALITY OF LIFE AND NEED FOR PSYCHOSOCIAL COUNSELLING

With advancements in diagnostic and treatment approaches and with the availability of state-of-art facilities, childhood cancers are now curable in majority of the cases. Hence, children have decades of life ahead after cancer, and challenges in treatment now encompass ensuring normalcy of future life. A treated child therefore should culminate into a socially productive person. Unfortunately, the childhood cancer experience predisposes long term survivors to a variety of chronic health problems, diminished health status, including functional impairment, activity limitations and quality of life deficits.

To overcome the sequelae of disease and prolonged treatment, it is important that the treatment duration should be a pleasant experience. Children should have availability of play and group discussion activities and academic curriculum in parallel with peer group, weekly assignments, hospital and home bound teaching throughout the course of treatment. These educational activities as well as access to counsellor, aid in resolution of many unaddressed queries and help them not only to feel engaged, normal and happy but also scholastically at par.

The resilience of the human body, mind and spirit is remarkable. As survivors of childhood cancer and their families experience these social problems, they should be cared for and counselled during treatment to reduce these after effects. They should be encouraged to seek help for these problems as most of these can be overcome with simple interventions.

*(Dr Kunal, DNB Student; Ms Pankaj Verma, Counsellor, Dept of Pediatric Hematology & Oncology)*



## PERSPECTIVE

### VALUE OF FLOW CYTOMETRIC ANALYSIS IN PEDIATRIC HAEMATOLYMPHOID NEOPLASMS

#### Introduction

Flow cytometry is the measurement of cellular (cyto) properties as they (cells) are moving in the fluid stream (flow) past a stationary set of detectors. Advancements in the technologies has enabled cells of different subtypes to be sorted and collected for further analysis. This analysis is called immunophenotyping, which is done by using fluorescence labeled antibodies to identify cells by detecting specific antigens expressed by these cells, called markers. These markers are usually functional membrane proteins involved in cells communication, adhesion or metabolism. Immunophenotyping using flow cytometry has become the method of choice in identifying and testing cells within complete population.

Nowadays flow cytometric immunophenotyping has become an important method in the diagnosis of haematological malignancies as it facilitates accurate diagnosis in both leukemias and lymphoid proliferative disorder, besides throwing light on some information regarding progress of therapy. Over the past two decades, advancement in instrumentation, software analysis, tools and in the availability of multitude of new flourochromes, has made the journey from single colour, immunophenotyping to multicolor or multiparametric immunophenotyping a smooth transition.

#### Principles

Commonly used flourochromes for antibodies confirmation are fluorescein isothiocyanate (FITC), phycoerythrin (PE) and allophycocyanin (APC). These flourochromes have been selected for maximum resolution, stability and ease of use. Nowadays since modern flow cytometers have two sources of light (LASER), one in blue region and the other in the red range in order to limit the spectral overlap out of the three flourochromes, ie APC, FITC and RPE. This aspect of the panels makes compensation as easy as for the conventional FITC and RPE two colour reagents.

Cell markers are also called CD (cluster diagnosis) markers and are commonly used for detection in flow cytometry and specific immune cell populations and

subpopulations. However, they will often be expressed on more than one cell type. Therefore, flow cytometry staining strategies have led to methods for immunophenotyping cells with two or more antibodies simultaneously. By studying such cell markers using several antibodies together, each coupled with different fluorochrome, a given cell population can be identified and quantified.

#### Procedure

Before starting the assay, comprehensive understanding of the normal expression patterns of an antigen and its relationship to the expression of other relevant antigens is necessary to perform high quality immunophenotyping. The presence or absence of antigen and intensity of some of the markers are also important factors for correct identification of cell lineages as well as for their subsequent subtyping. Therefore, selection of right combination of antibodies for the multiparametric analysis is essential.

Most of the users are adopting two panel policies for any samples, unless there is an excellent histomorphological backup. The panel consists of 2 lines. The first line, the initial screening panel, allows the screening for the presence of normal hematopoietic cells and malignant cells population. The second line is for the detailed classification of the cell types, thus giving good sub-classification in most of the leukemias and lymphomas.

The use of multiple antibodies per tube requires fewer tubes and thereby less patient material. This is crucial in certain cases where the number of cells available for analysis are few, such as leukopenic patients or where the marrow is not yielding good cellularity due to underlying fibrosis or in pediatric populations. The obvious advantages of multiparametric immunophenotyping is the simultaneous detection of multiple markers on distinct cell populations, resulting in a more rigid and objective detection of aberrant antigen expression as well as easy detection of heterogeneity and clonality of the malignant cells. Though the selected few workers in the world of flow cytometry are using upto 17 parameters, given its complexity, it is not recommended to use more than 5 colours for routine diagnostic purposes.

#### Indications

According to the 2006 Bethesda, international recommendations on the immunophenotypic analysis of haematolymphoid neoplasia, indications for flow

cytometry are more clinical presentations oriented, and include lymphocytosis, monocytosis and eosinophilia. Presence of atypical cells or blasts in the blood or bone marrow or body fluids, to involve the few and common ones.

### Flow Cytometry in Leukemias

**Acute Lymphoblastic Leukemia (ALL):** ALL is primarily a disease of childhood. 75% of cases occur in children <6 yrs of age with incidence of 1-4.75/100000 persons/yr. Approximately, 85% being precursor B-cell type and remaining approximately 15% benign precursor T-cell type. While B-lymphoblastic lymphoma is ~10%, of all lymphoblastic lymphoma, remaining being T-lymphoblastic lymphomas. These cases show positivity for B-cell markers. like CD19, cyto CD79a, CD22, CD10, CD24, Pax5, TdT in most cases, there being bright co-expression of CD10 and CD19 along with either CD34 and TdT or low density of CD45. While CD20 and CD34 expression are variable along with variable expression of myeloid associated antigens as CD13 and CD33 in some cases, this being commonest phenotype of precursor B-ALL.

If CD10 is absent, CD19 and CD22 are bright positive in presence of CD34 and/or TdT, this can still be called B-ALL. Co-expression of CD10 and CD19 along with CD24 and TdT or low density of CD45 is also considered to be B-ALL. Among this group, there is a subset of ALL with MLL translocations, especially in <1 yr age pediatric population who would lose CD10 and CD34 positivity. These patients have a very poor prognosis. There is another subset of ALL with t(12:21) (25% of ALL) showing frequent expression of CD13 the myeloid associated antigen, but has good prognosis. Lymphoblast in T-ALL/LBL are usually TdT positive and express CD1a, CD2, CD3, CD4, CD5, CD7 and CD8, of these CD7 and cCD3 are most oftenly positive but only CD3 is most specific (EGIL criteria, point-2). CD4 and CD8 are co-expressed on blasts. CD10 may be positive. Out of all T-ALL medullary T-ALL would be positive either for CD4 or CD8. CD1 expression on a T-cell lesion, along with TdT and/ or CD34 co-expression with cCD3 can also be considered diagnostic.

**Acute Myeloid Leukemia (AML):** AML can be diagnosed when an unequivocal aberrant pattern of myeloid or monocytic differentiations can be established. This would often include an increase in low intensity CD45 (+) and CD34 (+) cells, which express myeloid antigen and have low right angle scatter in combination

with cells expressing more mature markers of myeloid differentiations, including CD11b and/or CD15. Correlated displays which demonstrate aberrant expression of CD34 and/or CD117 (c-kit) and mature myeloid antigens, such as CD13 and CD33 when associated with high right angle scatter, also establish a diagnosis. There could be positivity for CD7, CD2 and CD4 or the B-cell antigen CD19 as aberrant expression.

### Detection of Minimal Residual Disease (MRD)

MRD is a small amount of disease usually post treatment that cannot be detected by routine morphologic examination of blood or bone marrow (BM). Over the last 2-3 decades, there has been an intense effort to develop methods to determine the degree of residual leukemic cells present in patients considered to be in morphologic remission (<5% blasts in the BM). Leukemic blasts in patients in morphologic remission following treatment cannot likely be differentiated from normal blasts present in marrow unless they have unique features, such as Auer rods. It is found that patients with even less than 5% leukemic blasts in their BM, can harbour as many as  $1 \times 10^{10}$  leukemic cells. Conversely normal hematopoietic progenitors (which may represent 5% or more of the cells in a regenerating BM) can be erroneously interpreted as residual leukemic cells. More sensitive techniques, such as molecular studies or flow cytometry are requested to detect MRD.

The value of MRD detection includes monitoring effectiveness of therapy; intensification or de-intensification of treatment; prediction and treatment of early relapse; better understanding of the mechanisms of drug resistance; as flow cytometric detection of MRD is the strongest prognostic factor in patients having ALL. In various studies, it is found that sensitivity of MRD by flow cytometry is  $10^{-3}$ - $10^{-4}$  with applicability for precursor, B-ALL and T-ALL of ~95% and with clear added advantage of being rapid (1-2 day turn around time) compared to molecular/PCR techniques.

### Future Perspective

The advent of microfluidic and nanofluidic technologies (Lab-on-a-chip, LOC) is one of the most innovative cytometric approaches to the analysis of rare cells and its organelles. Further diversification of this application is Raman spectral flow cytometry, especially to study programmed cell death-apoptosis finding its way in the tumorigenesis.

(Dr Sarika Singh, Haemato Pathologist; Dr Anurag Mehta, Chief of Laboratory Services)

## IN FOCUS

### ADVANCES IN PEDIATRIC CANCER TREATMENT AND CURRENT CHALLENGES

#### Introduction

The results of treatment of childhood cancer were poor fifty years ago, however presently these are very encouraging with overall cure rate of 70-80%. The credit goes to coordinated efforts by various scientific groups leading to better understanding of the biology of the disease. Further research is required to develop less toxic treatments for the curable pediatric cancers and newer approach for patients currently having dismal outcomes. Childhood cancers comprise a spectrum of malignancies that differ in histological type, site of origin, and incidence across age groups. Importantly, they also differ from adult cancers in significant ways. Whereas most adult cancers are epithelial and may be influenced by environmental factors (e.g., smoking and diet), most pediatric cancers are dysontogenic in nature. The purpose of this article is to highlight the advances already made in the field of pediatric oncology which have dramatically improved the results and look at the challenges currently faced in the treatment of advanced disease.

#### Solid Tumors

**Neuroblastoma:** The treatment of neuroblastoma currently is stratified based on the risk factors which include biologic features of tumor like DNA ploidy and MYCN amplification. While patients with tumors having favorable biologic features have excellent outcome, survival is suboptimal for patients with high risk features. Another notable point in treatment of neuroblastoma is the influence of age at presentation. Several studies have confirmed the improved outcome of patients diagnosed to have neuroblastoma in infancy. The recent studies have now reported continuing better survival for patients up to the age of 18 months. Neuroblastoma remains an interesting tumor as it can spontaneously regress or be fatal depending on the biology and age of diagnoses. Newer approaches are being investigated, including multiple autologous stem cell transplants and antiangiogenic agents.

**Wilms Tumor:** The improved outcome of Wilms tumor is one of the success stories of pediatric oncology. The current focus is to continue with the excellent survival rate

and decrease the morbidity of chemotherapy and radiation therapy. Although, there is difference in the timing of nephrectomy in North America and Europe, the outcome is excellent in both approaches. Radiation therapy is reserved for stage III tumors in National Wilms Tumor Study (NWTS) group approach. Adriamycin is added to the chemotherapeutic regime for stages III and IV only. Nephron sparing surgery is currently the standard of care for bilateral Wilms tumor after neoadjuvant chemotherapy. Addition of cyclophosphamide to patients with stages II-IV and diffuse anaplasia has shown improved 5-year relapse free survival. NWTS-5 identified loss of heterozygosity at chromosome 1p and 16q as an adverse prognostic factor and the future research will focus on reduction in treatment in the absence of unfavorable genetic findings.

**Rhabdomyosarcoma:** Over past 30 years, there continues to be improvement in the cure rates for rhabdomyosarcoma (RMS). Histologic features are important prognostic markers for rhabdomyosarcoma as is seen in neuroblastoma or Wilms tumor. Alveolar histology is an independent poor prognostic factor as compared to favorable embryonic histology. There is a clear difference in the outcome of patients with tumor at different sites with orbital, non-bladder/prostate genitourinary, non-parameningeal head and neck and biliary tract being the favorable sites. Several studies from Intergroup RMS Study Group (IRSG) have improved the multimodality treatment. Radiation therapy is eliminated or reduced for a select group of patients who have low risk RMS at favorable sites. Recommendations for surgery are to perform less aggressive resections which have maintained the cure rates. Future challenge is to improve the dismal prognosis in metastatic alveolar rhabdomyosarcoma. Targeted therapy against the gene fusion product of ARMS, PAX3-FKHR and PAX7-FKHR are being developed.

**Osteosarcoma:** Historically, localized osteosarcoma of an extremity was treated with amputation alone and most of these patients died of distant metastatic disease. In the mid-1980s, the role of chemotherapy was demonstrated. Current standard of care is neoadjuvant chemotherapy followed by surgical resection and adjuvant chemotherapy. The survival rate with this approach in localized osteosarcoma is currently approaching 60-70%. However, the results of metastatic osteosarcoma are still poor, especially if there are extrapulmonary metastases. Patients with osteosarcoma

metastatic to lungs, especially if they appear after long duration from completion of treatment, are treated by surgical resections and have good prognosis. The surgical principles entail en bloc resection of the tumor with adequate margins. Current practice is to perform limb salvage surgeries where the tumor is resected with adequate margins and skeletal reconstruction is done. Limb salvage surgeries are a challenge in skeletally immature child because there is discrepancy in the length of limb as the child grows. Some devices are now available which can be lengthened as the child grows.

**Ewing Sarcoma Family of Tumors:** With the advent of molecular pathology, Ewing sarcoma of bone, extraosseous Ewing sarcoma, and peripheral primitive neuroectodermal tumor are now characterized as a single tumor type as these tumors share the genetic lesion EWS-FLI1 [t(11:22)(q24;q12)]. Some Ewing sarcomas contain other translocations involving the EWS gene on chromosome 22. The EWS abnormalities may also offer a target for future therapies. Ewing's sarcoma was fatal before the introduction of systemic chemotherapy. Multimodality treatment which includes neoadjuvant chemotherapy followed by local control and then adjuvant chemotherapy currently has success rate of 60-70% cure in localized Ewing's sarcoma. Local control measures for Ewing's sarcoma are surgery, or radiation or both. While there is no controversy of choosing surgery as primary local control measure for expandable bones (rib, clavicle, fibula), radiation therapy is equally effective and chosen if the excision of tumor involves amputation. The treatment of patients with metastatic disease remains a challenge, and high-dose chemotherapy and immunotherapy regimens are under investigation.

### Haematolymphoid Neoplasms

**Acute Lymphoblastic Leukemia (ALL):** The treatment of ALL is a success story of pediatric oncology. This has been accomplished not by discovery of new drugs, rather by optimizing the use of available drugs by better understanding of pharmacokinetics and pharmacodynamics principles. Advances in molecular techniques have led to better characterization and risk stratification of patients at the times of diagnosis. Individualized treatment on basis of leukemia's genetic signature and detection of minimal residual disease has ensured the best treatment for every child. DNA microarray for global gene expression profiling of leukemic cells can predict treatment response and risk of relapse. Thus, it has become an important tool in

refining the treatment and identifying novel molecular targets, such as tyrosine kinase and FLT-3 inhibitors. Central nervous system (CNS) prophylaxis is an integral part of ALL treatment in addition to induction, consolidation and maintenance therapy. Although craniospinal irradiation is a very effective modality for CNS prophylaxis, it is associated with acute and long term neurocognitive sequelae and risk of secondary brain tumor. With careful modification of treatment using high dose methotrexate and intrathecal therapy, most of the children can now be effectively treated without radiotherapy.

**Hodgkin's Lymphoma (HL):** HL is another highly curable disease and we have come a long way since the 1970s, when radiotherapy was the mainstay of treatment. It was soon thereafter realized that radiation is associated with significant musculoskeletal late effects, risk of secondary cancer and endocrinopathy. Most contemporary regimens now use combined modality approach with chemotherapy and selective use of radiotherapy. Diagnostic imaging has obviated the need of staging laparotomy and use of PET-scan has increased the sensitivity of accurate staging, response and follow-up. With the multidisciplinary approach and effective combination chemotherapy, the cure rate of HL has exceeded 90%, and the primary aim of ongoing current trials is to reduce the short term and long term toxicity without compromising the efficacy with risk adapted and response based therapy.

**Non-Hodgkin's Lymphoma (NHL):** Pediatric NHL is a diverse group of high grade, heterogenous malignancies which are often associated with extranodal disease. The mainstay of conventional treatment is tailored to histological subtype and clinical stage of disease. The T-lymphoblastic subtype is treated on lines of ALL protocol, while B subtype is treated with multiagent, short course, non cross resistant chemotherapy. With multi-institutional cooperative groups, such as COG, BFM and LMB, outcome of the children with NHL has improved substantially. Newer therapies that target immunological aspect of lymphoma, such as rituximab, CD20 monoclonal antibody, are being recognized.

### Supportive Care

Optimization of supportive care is an essential and challenging component of oncological services. Most of the children with cancer present with life threatening metabolic/infectious emergencies or may develop these during the course of the treatment. Discovery of

rasburicase has significantly reduced the complication of tumor lysis syndrome and obviated the need of dialysis. The armamentarium of systematically administered antifungal compounds has expanded from amphotericin B to newer generation of triazole and echinocandins.

### Conclusion

In 1970s, childhood cancer was uniformly fatal. With the advances in scientific technology coupled with organized clinical trials of different Euro-American cooperative groups, the prognosis of childhood cancer has substantially improved. Risk and response based approaches will lead to better quality of life among survivors of childhood cancers. Further progress will require greater coordinated efforts to develop newer less toxic therapies for more curable malignancies and novel targeted approaches for patients at greater risk.

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

### PAIN AND PALLIATION IN CHILDHOOD CANCER

Pain in children with cancer is usually related to the disease or to its treatment. Palliation of pain is an essential component of comprehensive care of children with cancer. Unrelieved pain places an enormous burden on children and families. Children become afraid of future pain, and develop mistrust and fear of hospitals. They may feel victimized, depressed and their capacity to cope with cancer treatment may be impaired.

Pain management must begin when a child is first diagnosed with cancer and must continue throughout the course of the illness. Practical cognitive, behavioral, physical, and supportive therapies should be combined with appropriate drug treatment to relieve pain. Where possible, the cause of the pain should be determined and treatment of the underlying cause initiated. The WHO "analgesic ladder" should be used for selecting pain relief drugs in a step-wise approach to pain management in which the severity of child's pain determines the type and dose of analgesics.

Palliative care for children dying of cancer should be part of a comprehensive approach that addresses their physical symptoms, psychological, cultural, and spiritual needs. It should be possible to provide such care in children's own homes should they so wish.

### HOPE IN BATTLE AGAINST CHILDHOOD CANCERS

**Benefitting from Clinical Trials:** Clinical trials allow doctors to systematically study and compare treatments—including the side effects they cause—so that therapy can be refined and improved. In fact, most children with cancer in the United States are now benefiting from clinical trials.

**Rising Survival Rates:** Before the 1970s, less than 50% of children with cancer survived 5 years after diagnosis. Today, around 80% of kids make it to the 5-year mark. Five-year survival rate for acute lymphoblastic leukemia in kids under 15 has risen from about 61% in 1975-1978 to more than 88% in 1999-2002. Likewise, the survival rate for kids under 15 with acute myeloid leukemia increased from less than 20% in 1975-1978 to 58% in 1999-2002. Other cancers with survival rates that rose between the 1970s and the 2000s include non-Hodgkin lymphoma (now 88%), Hodgkin lymphoma (about 95%), Wilms tumor (over 90%), and the brain tumor medulloblastoma (73%).

**Supportive Care Key:** More effective pain treatments, antiemetics, antifungal medications and antibiotics helped to boost survival rates and improved quality of life for kids during and after treatment of any kind of cancer.

**International Cooperation on Uncommon Cancers:** There is a growing trend towards international collaboration in research on the rarer cancers that experts hope will spur progress.

**New Therapies Needed:** New therapies like chemotherapy with better formulations, longer-acting ones, less toxic drugs, targeted and personalized therapy are desperately needed to make the next big improvement in the outlook for children with cancer.

**Gene Sequencing:** Another area of intensive research is gene sequencing – looking for the specific DNA mutations that occur with different types of cancer. Identification of these mutations will provide information that could lead to new treatments.

It is expected that these new avenues of research and collaboration would pay big dividends. Pediatric oncologists are overall curing almost 75% to 80% of all children combined. In the coming decade, it is expected to approach 90%.

(American Cancer Society News, Sep 1, 2010)

## NEW TECHNOLOGIES

### A Big Leap for Neuroblastoma

Study led by researchers at the Children's Hospital at Philadelphia found that an aggressive new treatment with immunotherapy has improved two years survival in children with high-risk neuroblastoma by 20 percent compared to standard care, the first substantial increase in cure rate in this group for over a decade. Neuroblastoma is a cancer of the nerves outside the brain and usually starts in the adrenal glands. It typically develops early, with a significant number of cases in children less than a year old. About half the kids with neuroblastoma have high risk form of the disease. This form of disease often returns after initial treatment, so the prognosis is usually poor. The normal course of therapy for high risk neuroblastoma includes surgery, chemotherapy, radiation, a transplant of the patient's own stem cells and retinoic acid.

The researchers found that immunotherapy with Ch 14.18, a monoclonal antibody along with granulocyte-macrophage colony-stimulating factor and interleukin-2 was associated with a significantly improved outcome as compared with standard therapy in patients with high-risk neuroblastoma. It was superior to standard therapy with regard to rates of event-free survival ( $66 \pm 5\%$  vs  $46 \pm 5\%$  at 2 years,  $P=0.01$ ) and overall survival ( $86 \pm 4\%$  vs  $75 \pm 5\%$  at 2 years,  $P=0.02$  without adjustment for interim analyses). There are lots of side effects, so the patients must be monitored carefully while they are receiving treatment in the hospital.

*(N Engl J Med, Sep 30, 2010)*

### Dexrazoxane for Cardioprotection

Doxorubicin chemotherapy is associated with cardiomyopathy. To establish the long term effect of dexrazoxane on the subclinical state of cardiac health in survivors of childhood high risk acute lymphoblastic leukemia (ALL) 5 years after completion of doxorubicin treatment, children with high-risk ALL were enrolled from nine centres in the USA, Canada and Puerto Rico. Patients were assigned by block randomization to receive ten doses of  $30 \text{ mg/m}^2$  doxorubicin alone or the same dose of doxorubicin preceded by  $300 \text{ mg/m}^2$  dexrazoxane. Dexrazoxane provided long-term cardio protection without compromising oncological efficacy in doxorubicin-treated children with high-risk ALL. The

primary endpoints were late left ventricular structure and function abnormalities as assessed by echocardiography. Results showed that the protective effect of dexrazoxane, relative to doxorubicin alone on left ventricular wall thickness and thickness-to-dimension ratio, was the only statistically significant characteristics at 5 years. Subgroup analysis showed dexrazoxane protection for left ventricular fractional shortening at 5 years in girls but not in boys. Similarly, subgroup analysis showed dexrazoxane protection for the left ventricular thickness-to-dimension ratio at 5 years in girls, but not in boys.

*(The Lancet Oncology, Oct 2010)*

### Endoscopic Procedure for Brain Tumor

Revolutionary endoscopic procedure developed by the surgeon from Los Angeles can now safely excise the pineal tumor, which is one of the most difficult-to-remove tumors located deep in the midbrain area. Pineal tumors are most common in children than adults (average age of diagnosis is 13) and can be problematic as they can press on nearby brain structures causing painful and serious reactions. These tumors can cause headache, nausea, fatigue, visual impairments, double vision, memory problems, seizures and, in children, precocious puberty. The minimally invasive approach involves making a dime-size opening behind the ear, inserting a small endoscope over the top of the cerebellum and through a natural pathway accessing the deep seated pineal tumor. Patients operated so far are enjoying healthier asymptomatic lives. More invasive open brain approach, favored by neurosurgeons, leaves patients more vulnerable to brain damage and other side effects as well as long and difficult recoveries. For patients suffering from significant symptoms, open brain surgery is often the first option. When surgery is required, this minimally invasive approach is an excellent and safe alternative and results in much shorter surgery and hospitalization times and fewer complications.

*(Frank Groff Inc, Sep 21, 2010)*

### Novel PEGylated DNA Topoisomerase 1 Inhibitor

PEG-SN38 (EZN-2208) is a novel PEGylated DNA topoisomerase 1 inhibitor developed by Enzon Pharmaceuticals, Inc. SN38 is the active metabolite of the widely used cancer drug irinotecan, marketed as Camptosar® in the US. Although unmodified SN38 is 1000 times more potent than CPT-11 (irinotecan), it has not been converted into a viable drug candidate

because of its insolubility. Using Enzon's proprietary customized linker-enhanced PEGylation technology, the company developed PEG-SN38, which results in a compound with excellent pharmaceutical properties: increased solubility, higher exposure, and longer half life than unmodified SN38. It may be administered weekly or once every three weeks. PEG-SN38 is being evaluated in metastatic breast cancer, metastatic colorectal carcinoma and pediatric patients with solid tumors and lymphomas. Preclinical data demonstrated that PEG-SN38 in pediatric neuroblastoma has led to significantly greater tumor regression as compared to CPT-11 in both in vitro and in vivo models. PEG-SN38 was found to be 100-fold more potent than CPT-11 in vitro. In vivo, treatment with PEG-SN38 resulted in no detectable tumor at the end of studies, whereas only minor therapeutic effect was observed with CPT-11.

*(Enzon Pharmaceuticals, Inc, Oct 7, 2010)*

### **Robotic Drug-Screening Technology**

Research is entering the dawn of a new era with the appearance of robotic drug-screening technology, which is a part of a wider push towards personalized medicine. New Technology is poised to accelerate progress, using superfast robots that can do in days what it would take teams of technicians 12 months to complete. Experts at the Australian Cancer Research Foundation and Children's Cancer Institute Australia (CCIA) have launched a new \$3.1 million Drug Discovery Centre at the University of NSW, where one such robot would be used to rapidly hunt through "libraries" of molecules in the hope of finding one that has a high likelihood of achieving a specific objective, such as blocking a previously identified cancer causing gene. Such molecules, once found, still have to go through the painstaking process of being turned into a useful drug. Through manual methods, researchers have already spent six years developing reversan, a potential drug for neuroblastoma to switch off MRP-1 gene, which is found in high levels in patients with aggressive neuroblastomas. New robot would increase the speed quite dramatically with which researchers can undertake drug discovery for children's cancer. It can screen 20,000 compounds a day. The CCIA's technology would focus on childhood cancer applications and would also be available to the wider science community.

*(UICC News, Aug 28, 2010)*

## **GLOBE SCAN**

### **Good Follow-Up Healthcare**

A study of Australian childhood cancer survivors has laid emphasis on the need for 'good follow-up healthcare' for these survivors, since they still face a high risk of cancer later in life or may die early of other causes. It observed that the childhood cancer survivors had an almost five-fold increased rate of developing a new cancer in comparison with the overall New South Wales population and were about 7.5 times more likely to die early. It is important for cancer survivors to be aware of the risk factors for complications of treatment and second cancers, and maintain good follow-up healthcare. There is an underlying genetic basis for the way patients respond to cancer treatment. This same genetic variation is likely to contribute to these long term effects of cancer therapy. If genetic factors are mapped, more individualized cancer treatments can be developed that do not result in long term health complications.

*(Australia: The Medical J of Australia, Sep 6, 2010)*

### **To Step Up Childhood Cancer Fight**

In the United States, Panels of the internationally renowned doctors and researchers joined Congressmen at their Childhood Cancer Summit on Capitol Hill to emphasize the unique challenges facing childhood cancer patients and their families compared with adult cancers, to increase awareness among members of Congress to advance policies as well as increase funding in the fight against the disease. Studies and drug development specific to pediatric cancers remain underfunded. The most pressing need is research and development of new treatments, which cure more children and cause fewer side effects and ensure the best chance to live long, healthy lives. Congressmen would roll the panel's recommendations into a legislative agenda that includes: incentives for drug development, grants for specialized training to primary care physicians to better identify side effects and re-occurrence of symptoms, greater access to clinical trials, greater emphasis on survivorship and impact of childhood cancer on families and full funding of the Caroline Pryce Walker Conquer Childhood Cancer Act to increase pediatric cancer research and create a pediatric cancer registry at the Center for Disease Control.

*(US: Medical News Today, Sep 17, 2010)*

## IMMUNIZATION IN CHILDREN WITH CANCER

Vaccination represents a crucial approach for preventing infection in immunocompetent individuals. In children with cancer, the method of prevention should be tailored to the specific needs of each patient based on his or her underlying disease, nature of treatment, host defense, epidemiologic exposures and age of child.

### A. What You Should Know Before You Immunize Children Undergoing Treatment for Cancer?

1. Children undergoing treatment for cancer are immuno-suppressed due to:
  - a) Cancer itself, particularly leukemia and lymphoma can have an adverse effect on immune function;
  - b) Cancer therapy with alkylating agents, antimetabolites, radiation;
  - c) Patients undergoing bone marrow or solid organ transplantation; and
  - d) Those treated with large amounts of corticosteroids.
2. Immunocompromising conditions may alter vaccine recommendations in several ways for the following reasons:
  - a) Reduced antibody response to immunization and hence requirement of higher dose, additional boosters, or post immunization serologic testing for immunity (eg, hepatitis B virus vaccine). The immune response, however, may remain sub-optimal, even with these modifications;
  - b) Viral replication after administration of live attenuated virus vaccines can be enhanced and may pose a risk to immunosuppressed patients. In general, killed or inactivated vaccines do not represent a danger to immuno-compromised persons.

### B. Should You Immunize Children Undergoing Treatment for Cancer?

The only vaccination we routinely recommend for children undergoing treatment for cancer is the recombinant Hepatitis B, if previously not immunized and/or if titre is low.

### C. When to Immunize Children Undergoing Treatment for Cancer?

1. Children treated with standard dose chemotherapy:
  - a. Killed or inactivated vaccines may be used 6 months after completion of chemotherapy;

- b. Generally live attenuated vaccines are safe at least one year after completion of therapy.
2. Children who have undergone hematopoietic stem cell transplant:
  - a) For patients who have undergone allogeneic bone marrow transplant, killed vaccines can be given 12 months post transplant;
  - b) Live vaccines can be given 18-24 months post allogeneic bone marrow transplant.

Passive immunoprophylaxis with immunoglobulins may be indicated for immunocompromised persons instead of or in addition to vaccination. When exposed to a vaccine-preventable disease, such as measles and chicken pox, severely immunocompromised person should be considered susceptible regardless of their history of immunization.

### D. Recommendations for Household Contacts of Immunosuppressed Children

1. Contraindicated vaccines– Oral polio vaccine is contraindicated because viral shedding may occur for 8-12 weeks and intravenous polio vaccine should be given instead.
2. Recommended vaccines– All routine age appropriate vaccines should be administered. Varicella vaccine is recommended in all household contacts with a negative history of varicella zoster infection.

(Dr Akanksha Chichra, DNB Fellow; Dr Gauri Kapoor, Sr Consultant, Dept of Pediatric Hematology & Oncology)

## NUTRITION IN CHILDREN WITH CANCER

- Treatments like chemotherapy, radiation or surgery for childhood cancer can affect appetite.
- Treatment side effects can cause nausea, unusual allergies and mouth sores as well as changes to the sense of taste.
- Nutritional care that helps patients achieve normal growth and weight gain and continuing normal activities is important to overall well-being.
- Nutrition as a treatment can speed recovery and reduce the incidence of medical complications, thereby decreasing the number and duration of hospital stays as well as need for medications and other treatments.
- The dietitians routinely consult with other members of the medical team to determine the best course of nutrition therapy for patients receiving treatment.

([www.stjude.org](http://www.stjude.org), Nov 22, 2010)



**CHILDHOOD CANCER:  
TIPS FOR GENERAL PRACTITIONERS**

**Introduction**

Childhood cancer is uncommon but remains the leading cause of disease-related deaths in children. Early diagnosis is critical, as survival rates have increased dramatically over the past decades. Prolonged delay in diagnosis is common. When one encounters symptoms suspicious for a childhood malignancy, it is imperative that the child be referred to a pediatric cancer centre. These centres possess not only the ability to further evaluate and manage children with malignancy, but also are able to provide support for patients and their families.

**Key Issues for Early Diagnosis**

**High Index of Suspicion:** Childhood cancer can be difficult to diagnose in the primary care setting. The index of suspicion tends to be low because of the relative rarity of malignancies in children. Furthermore, the presenting signs and symptoms are often non-specific and mimic those of common childhood conditions, such as viral infections. So, one has to be vigilant to pick up these relatively rare but potentially curable malignancies. Age of the child provides an important clue to the possible diagnosis. For example, neuroblastoma, retinoblastoma and Wilms tumor most commonly occur in children between birth and four years of age, whereas osteosarcoma, Ewing’s sarcoma and Hodgkin’s disease tend to occur in children more than 10 years of age.

**Recognizing High-Risk Groups:** (i) Children with neurocutaneous syndromes; (ii) Children with chromosomal disorders including Down’s syndrome,

Fanconi’s anaemia and other chromosomal break syndromes; (iii) Children with immunodeficiency states are especially prone to lymphomas; (iv) Children with a history of a previous malignancy, cirrhosis and whose siblings had a malignancy; (v) Children with congenital malformations and syndromes including children with Beckwith-Weidman syndrome; (vi) Children with aniridia (absent iris) and hemi-hypertrophy.

**Recognising the ‘Red Flag Signs’ of Childhood Cancer:** At least 85% of pediatric cancers are associated with this group of signs and symptoms. The remaining 10-15% present with unusual signs or symptoms and are difficult to diagnose. These should alert the general practitioner about the possibility of a malignancy.

**Difference Between Childhood & Adult Cancers**

1. One of the major ways in which childhood cancer is different from adult cancer is that childhood cancer can be **cured** (>70-80%) more often than in adults. Even though over 95% of all cancers occur in adults and less than 5% occur in children, the last 30 years of research have produced dramatic improvements in survival rates of childhood cancer.
2. Children get cancers that affect the **stem cells** (like acute lymphoblastic leukemia, embryonal rhabdomyosarcoma, Ewing’s sarcoma, nephroblastoma, hepatoblastoma etc). These cells are relatively simple and undifferentiated and very **sensitive to chemotherapy**. Adults on the other hand are more likely to get epithelial cancers which are quite differentiated and are less responsive to chemotherapy.
3. Most childhood cancers appear to be the result of **genetic accident** that occurs spontaneously in cells after birth and not due to environmental or nutritional

**Early Diagnosis of Childhood Cancer: Red Flag Signs**

Symptom	When to Evaluate	Test
Fever	Fever lasts longer than 14 days with no identifiable cause.	Complete Blood Count (CBC) with differential count
Lymphadenopathy	Evaluate if lymphadenopathy does not respond to a 7-day course of antibiotic and size is more than 1cm.	CBC, with differential count, lymph node biopsy
Vomiting	Vomiting lasts longer than 7 days with no identifiable cause. Vomiting is associate with headache during sleep	Computed Tomography (CT) head
Abdominal or testicular mass	Even if it is asymptomatic and incidently identified	Ultrasound (USG) abdomen and tumor markers
Cough	Cough is prolonged (>2 weeks) and has no identifiable cause	Chest radiograph
Bone or muscle pain	Pain is prolonged (>2 weeks) and has no identifiable cause	Plain-film radiograph, bone and CT scans
Headache	Headache occurs during sleep, is associated with neurologic signs and vomiting, or occurs in the absence of a family history of migraine.	CT head
Hematuria	Evaluate immediately if hematuria has no identifiable cause.	USG abdomen
Voiding difficulty	Evaluate immediately if voiding difficulty has no identifiable cause.	USG abdomen

factors. In adults cancer is usually induced by interaction with the environment.

4. Another important difference is that children with cancer are generally more resilient than adults and therefore can **tolerate more aggressive therapy**. Adults on the other hand often have many other health problems like high blood pressure, heart disease, diabetes etc that make it more difficult to treat them aggressively.

### Childhood Cancer Treatment at RGCI&RC

1. Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC) is unique in India as it offers **comprehensive oncology care to all children up to the age of 18 years**. It is a place where doctors send some of their most challenging and sick patients. The department has a dedicated team of experts in the field of pediatric hematology/oncology. The team constituted by experienced pediatric oncologist, hematologist, pediatric onco surgeon, radiation oncologist, pediatric oncology residents and nurses, child psychologist and playroom teacher, work hard to ensure that best care is delivered to every child.

2. The Institute routinely treats all types of childhood cancer, including acute leukemia (acute lymphoblastic leukemia and acute myeloid leukemia), lymphoma (Hodgkin's and Non-Hodgkin's) as well as solid tumors (brain tumor, neuroblastoma, Wilms tumor, soft tissue sarcoma, osteosarcoma, retinoblastoma, etc). In most childhood cancers, chemotherapy is the mainstay of treatment. Surgery and radiotherapy are also required but limited to very specific situations.

3. The treatment is tailored to diagnosis and stage of disease (**Risk stratification**). With pediatric cancer now being curable, the goal is to try and reduce long-term sequelae and provide the cancer survivors with a good quality of life.

4. The Institute has the entire **supportive infrastructure** required. As we increase the intensity of chemotherapy, we cure more children. However this also increases the side effects. Aggressive supportive care includes the use of appropriate antibiotics to treat infections that can even be fatal, if neglected. Use of growth factors to support the counts and blood component therapy are also critically important in treating pediatric cancer patients. The excellent survival of these children would not be possible without the newer antibiotics and modern blood banking techniques. Trained nurses in pediatrics as well as oncology and intensive care are equally important in achieving these good results.

Quality patient care remains at the core of our mission, and it is the hallmark of our department. It is believed that families are essential in providing the best physical and psychosocial care for their children. We know that the family is a child's prime source of strength and support. Patients and families are supported by:

- i) Helping children, siblings or families adjust to illness
- ii) Conducting individual and family psychotherapy
- iii) Offering a variety of support groups and education programs for parents and siblings
- iv) Engaging patients with therapeutic play, art therapy and music therapy
- v) Connecting families to various financial resources
- vi) Easing the transition from hospital to school
- vii) Offering supportive services for end-of-life issues

Recognizing the special needs of children with cancer, the hospital has designated areas for pediatric patients. In the outpatient area, there is a special clinic for children with separate waiting area and a Pediatric Daycare facility (for outpatient short term chemotherapy and blood transfusions) manned by pediatric nurses. The in-patient area has two pediatric wards as well as a playroom for children. The bone marrow transplant unit is well equipped to handle pediatric autologous and allogeneic bone marrow transplantations.

### Worth of Treating Cancer in Children

Treating children with cancer has been a rewarding task, not only because of the improvement in cure rate, but also because research has provided better understanding of the disease as well as its treatment. We are optimistic that as knowledge grows, we will be able to further refine treatment and target therapy to specific genetic lesions. It is noteworthy that curing a young child saves a greater number of productive life years, since a five-year old may have sixty or more years to live after being cured, while adults may have only a few more years of life succumbing to some other illness.

### Conclusion

To make childhood cancer curable, it is not enough that we possess all the scientific information and latest technology, it is equally important that the children are diagnosed in time, treated in an experienced pediatric oncology unit and families ensure that complete treatment is taken, as per the advice of the treating doctor. Best results depend upon early referral by the thoughtful practitioner.

*(Dr Sandeep Jain, Clinical Assistant; Dr Gauri Kapoor, Sr Consultant, Dept of Pediatric Hematology & Oncology)*