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EDITORIAL

CELEBRATING 25 YEARS OF RGCIRC

"Everything starts with an idea, a concept in the mind. A dream is shaped by actions. Actions become reality by sincerity and hard work. People say miracles happen to those who believe in them." Rajiv Gandhi Cancer Institute and Research Centre is that miracle which was conceptualized by Sh.K.K.Mehta and few like minded people such as Sh. AVM HKL Kapoor, Sh. ACM OP Mehra and Sh. OP Nayar in 1990. Rajiv Gandhi Cancer Institute and Research Centre saw the light of the day on 1st July 1996.

Twenty five years on Rajiv Gandhi Cancer Institute and Research Centre is leading 500 bedded cancer hospital of north India, with state of the art facilities and tech - savvy People. It now houses fourteen modular ot's, a BMT unit, three ICU's, a well-equipped lab including a molecular lab and a blood bank with component facility. We have acquired 2 PET-CT machines, state of the art radiotherapy machines and established interventional radiology department. It has been our constant endeavor to improve the quality of cancer care. Today we recall 25 years of its journey of growth from infancy to adult hood.

Our patients and caregivers are not merely clients or contacts; they form the core of our ethos. We have built our relationships with them which is beyond clients or contacts. For our doctors, nurses and other staff members, the institute is not just a place of work, it is their identify, their second home. Care with empathy has become the USP of this institute. We try and live up to the founding principles of ethics and empathy as much as we can on every single day of our work at this institute. This institute is not just a building with splendid machines, it is a hospital with a sound heart. We pray that RGCIRC continues its journey towards excellence in cancer care.

In 2007 Rajiv Gandhi Cancer Institute and Research Centre decided to go into subspecialties within surgical oncology. Seven subspecialties (now nine) were created. Head & Neck, Breast, Gynae, Uro-Oncology, Thoracic, GI oncology, Ortho, Neuro Oncology and Reconstructive Surgery. Surgeons were quite apprehensive of being confined to single speciality and in the process lose out few of the patients. But in this bargain, we developed better surgical skills, procured the best equipments, technology, manpower and achieved better results. Within each subspecialty, we institutionalized good protocols and adopted NCCN guidelines.

Rajiv Gandhi Cancer Institute and Research Centre is a unique oncology center with subspecialties within a specialty service. On lines similar to surgical oncology, radiation and medical oncology services were also divided into subspecialties. Medical oncology now has Hematology, Breast, Thoracic, GI, GU medical oncology services parallel to surgical oncology. Radiation oncology also imbibed similar culture and developed head & neck, thoracic, GI, GU, breast radiation oncology units. There after we formed site specific clinics consisting of Breast Medical Oncology, Breast Surgical oncology and Breast radiation oncology. Even Pathology and radiotherapy Departments specialized in site specific services. Department of lab services developed molecular lab acquiring latest technologies eg. NGS, RT-PCR, FISH etc.

Fourth dimension of oncology in the form of "Interventional Oncology" was started in 2018 with various diagnostic and therapeutic interventions. Research wing of Rajiv Gandhi Cancer Institute and Research Centre gave thrust to better understanding of cancer biology. A biorepository was set up for preservation of tumors and blood samples for ongoing and possible further research at molecular level.

In the recent past, emergence of innovative I.T. technologies have rapidly changed the entire ecosystem. Electronic health record systems are increasingly being used. Imaging Systems are also being endowed with communication capabilities so that medical images can be directly sent to a central imaging repository (a Picture Archival & Communications System, PACS). The PACS allowed for easier handling of medical images and made them available to a physician on demand, and remotely. AI (Artificial Intelligence) is bringing Radiology and Pathology to a much greater convergence. Future of the diagnostics seems progressing very much on this line.

The founders of RGCIRC embraced their collective pain and burnt it as fuel for their journey that started with a dream and transformed into reality that is RGCIRC. In last 25 years it has become one of the finest facilities in cancer care in the country. Its multimodal and multidisciplinary care does not stop at advances in surgery, radiotherapy and medicines, it includes an ever willing ear, a shoulder to lean on, a kind word spoken, a small help given and a smile by all health professionals.

When I started my journey in RGCIRC on 1st July 1996, I believed I knew what sympathy and empathy meant. But new meanings unravelled with time. I interacted with senior management, my colleagues, subordinates, thousands of patients and caregivers and realized that essence of care is empathy. To that life affirming principle, I offer my gratitude with folded hands.

Dr. A. K. Dewan
Director - Surgical Oncology

RISK ADAPTED THERAPY IN HEMATOLOGY AND HEMATO-ONCOLOGY

These are times of evidence based and risk adapted treatment approach in every segment of medicine. There has been gradual evolution in diagnostics and therapeutic strategies over past decades to come to this era of risk adapted approach to treatment. With advances in diagnostics, we are now able to have a better classification and risk stratification of various hematological malignancies. Similarly, treatment strategies have evolved in such a way that now we treat some good risk patients with less intensified approach to minimize toxicities while maintaining efficacy of the treatment regimes and intensifying the treatment in only those with high risk disease.

Treatment of aggressive lymphomas: Commonest example of aggressive lymphoma is diffuse large B cell lymphoma (DLBCL) and high grade B cell lymphoma (HGBCL). Currently DLBCL is further classified into several subcategories based on its gene expression profile or immune-histochemical patterns which are surrogate to molecular features. These subclasses are germinal centre type (DLBCL-GC) which is considered a good prognostic class compared to other one, the activated B cell (DLBCL-ABC) type which has got a poorer prognosis. Another advance in the management of DLBCL and High grade B cell lymphomas is identification of re-arrangement of cMyc and BCL2/BCL6 genes detectable by Fluorescent in-situ hybridization (FISH) technique. Based on cMyc and BCL2/BCL6 gene rearrangements, DLBCL and high grade B cell lymphoma can be classified into double hit/ triple hit lymphoma (DHL/THL) and non double hit lymphoma. Double hit/ triple hit lymphomas are highly aggressive and are associated with poorer prognosis. Therapy is usually intensified in such patients to achieve better results.

High grade T cell lymphomas (except lymphoblastic lymphoma which is treated with ALL like therapy) are also treated with intensive chemotherapy and Autologous bone marrow/ hematopoietic stem cell transplantation in selected patients with high risk features.

This way, it is very much needed these days to identify high risk features by molecular testing. Intensification of therapy is warranted in selected patients with high risk features to achieve outcomes comparable to good risk patients while less intensified treatment approach is maintained for those with good risk disease to minimize toxicities while maintaining good outcomes.

Treatment of Multiple Myeloma: Multiple myeloma is also called Myeloma. Myeloma was once considered a deadly and incurable disease and was usually treated with cytotoxic chemotherapies. Over past two decades, there has been development of many anti-myeloma drugs with specificity for myeloma cells (malignant plasma cells) and lesser cytotoxicity to normal tissues. These drugs are Proteasome inhibitors like Bortezomib, Carfilzomib and Ixazomib and Immuno-modulators with anti-angiogeneic properties like Thalidomide, Lenalidomide and Pomalidomide most of which are available for Indian patients very easily and at affordable cost. Apart from these two major classes of drugs, now we have certain targeted therapies-immunotherapies like anti CD 38 monoclonal antibody (Daratumumab, Isatuximab), Anti SLAM F7 antibody (Elotuzumab) and anti BCMA antibody (Balantamab). Moreover, CAR-T cell therapy is promising and is in developmental phase in India. With cytotoxic therapies of past, complete remissions were uncommon and would be to the range of 30% even after an Autologous Bone Marrow Transplantation and an early relapse in majority of patients. But nowadays, with wide availability of novel agents, we are able to achieve complete remission and even deeper remissions in a significant majority of patients and that can be further improved with an Autologous Bone Marrow Transplantation and further maintenancetherapy. A part from expansion of this therapeutic armamentarium, there has been progress in understanding of cytogenetic and molecular patterns of myeloma and its prognostic and therapeutic implications. Now a day, FISH technique is widely available to identify cytogenetics aberrations specific to myelomaand we can identify high risk myeloma (for example, those with 17p [p53] deletion, 1q gain and others like t4:14, t14:16) with help of FISH. Taking together the clinical features and cytogenetic abnormalities, we can design treatment in such a way to achieve better results in even those with very high risk myeloma.

Acute leukemias: acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are most aggressive and deadly of hematological malignancies. Both AML and ALL are heterogenous diseases and varied widely in prognosis depending on cytogenetic and molecular profile. So, there are AML which are classified as good risk or standard risk (examples- AML with t8:21, inv16, normal karyotype with NPM1 mutated without FLT3 mutation or AML with normal karyotype with CEBPA double mutated) while others as high risk AML (examples- AML with complex karyotype or monosomal karyotype, t v:11q, monosomy 7/-7q, monosomy 5/5q-, AML with FLT3-ITD etc). Similarly, prognosis of ALL too depends upon several clinical and cytological factors. There are patients with good risk ALL (example- young age, lower WBC counts at presentation, hyperdiploid karyotype) while others with high risk ALL (example- advancing age, higher WBC counts at initial presentation, cytogenetic/ molecular features like t9:22/ BCR-ABL or t4:11/AF4:MLL). Patients with high risk leukemias not only show resistance to chemotherapy but also have a higher probability of relapse early in the course. Patients with good/ standard risk leukemias are usually treated with chemotherapy alone while patients with higher risk leukemias are usually offered chemotherapy to achieve initial disease control and then Allogeneic bone marrow transplantation as a consolidative therapy to minimize risk of relapse. We can use targeted drugs along with chemotherapies in patients having specific molecular aberration. For example, patient of ALL with BCR-ABL fusion are high risk and are treated with chemotherapy along with targeted drug (Imatinib/ Dasatinibwhich targets BCR-ABL gene) and this way achieve deeper remissions and better outcome. Similarly, FLT3 mutation (FLT3 ITD) confer chemo resistance in AML and nowadays is treated with targeted drug (Midostaurin/ Sorafenib) along with chemotherapy to achieve better outcome.

Bone marrow/ hematopoietic stem cell transplantation (BMT): A BMT is recommended for patients having bone marrow failure syndrome or with high risk hematological malignancies at high risk of relapse. There have been immense progresses in field of BMT over past decades. Several notable advances are matched unrelated donor transplants, haplo-identical transplants, non-myeloablative and reduced intensity transplants. This way, most of patients in need of a BMT can be taken including those with advancing age or those not having a suitable HLA matched stem cell donor in family

So in nutshell, we have come a long way to this era where we have sophisticated methods to dissect cytogenetic and molecular details of hematological malignancies, plan therapy as per risk stratification and use targeted therapies and bone marrow transplantation to get optimal outcome.

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RULE OF SIX FOR CRS AND HIPEC: AN INSTITUTIONAL EXPERIENCE

Introduction - We, on the basis of our experience of last 7 years at a tertiary care centre, tried to develop a standard protocol as **'RULE OF SIX IN HIPEC'** for the better understanding and management of this challenging procedure. This rule may help for the better outcomes of HIPEC procedures, practiced as six indications, six rationale, six criteria of patient selection, six contraindications, six advice before HIPEC, Six steps of checking before CRS, Six assessment for NACT, Six steps of surgery, six mechanism of action, six important complications, six advice in discharge, six important points to be clarified still. The observational data is based on the analysis of the surgical procedure and its outcome in 150 patients.

1. Diseases to be considered under PSM: Worldwide Six common indications for CRS & HIPEC. But, in carcinoma appendix with pseudomyxomaperitonei and mesothelioma CRS and HIPEC has been the standard of care. These malignancies are enumerated as follows.[1]

I. Carcinoma appendix with Pseudomyxomaperitonei
II. Mesothelioma
III. Colorectal cancer
IV. Ovarian cancer
V. Gastric Cancer with Peritoneal dissemination only
VI. Peritoneal Sarcomatosis

2. Rationale: literature suggests six reasons to be considered.

I. the disease is confined to the peritoneal cavity for a long time
II. Even in recurrent cases, disease remain confine to peritoneal cavity only.
III. Intra peritoneal administration of chemotherapy results in high peritoneal to plasma ratios for peak concentration of chemotherapeutic drugs.
IV. The higher peritoneal concentration improves penetration of cytotoxic agent in tumor microenvironment.
V. Less than 2 to 3 mm deposits have significantly higher chemotherapeutic drug exposure from IP administrations as compared to IV.
VI. Avascular tumours are exposed to higher drug concentration.

3. Patient Selection: Six Criteria to be followed:

1. Good performance status ECOG1 and ECOG 2 with optimisation.
2. Mentally and physically fit for extensive surgery.
3. Clinically, radio logically and biochemically the disease is low burden and resectable.
4. No Haematogenous and extra abdominal metastasis
5. Good renal function.
6. Age < 65 years with PFT (FEV1 > 1-1.5lts),non-smoker with complete blood counts, kidney function rests and liver function tests within normal limit.

4. Contraindications:

1. Poor performance status, i.e; ECOG ≥ 3
2. Patients is not willing for extensive surgery.
3. Signs and symptoms of active peritonitis and sepsis.
4. Clinically and radiologically high burden disease involving porta, root of mesentry, diffuse serosal deposits, disease burden not amenable for optimal cytoreduction.
5. Compromised liver, renal and respiratory function.
6. Age > 70 with cardiovascular compromise.

5. Preoperative Therapy: Indications for NACT before CRS + HIPEC, when;

1. Imaging suggestive of high tumor burden where upfront optimal CRS is not feasible.
2. Tumor ≥ 3 cm around portahepatis or around root of mesentry.
3. Intra hepatic metastasis or extra abdominal disseminated disease.
4. Where bowel resection is required more than 1.5 m due to extensive serosal or intra luminal involvement.
5. Possibiltyof ≥ 2 small bowel anastomosis after CRS.
6. Extensive retroperitoneal lymph nodes.

6. Optimisation: Patients to be optimised preoperatively by Six ways

1. High protein diet
2. Maintenance of hygiene.
3. Regular ½ hour to 1 hour mild to moderate physical exercise.
4. Incentive spirometry 200 times/day.
5. Haematinics to optimise haemoglobin
6. Adequate hydration 2.5- 3 litresof liquids inclusive of water per day to keep the renal function normal.

7. Intraoperative Assessment of disease

1. Overall disease burden at primary site
2. Involvement of bowel bladder and it extend.
3. Root of mesentery and small bowel involvement.
4. Exclude the liver and spleen involvement
5. Sub diaphragmatic involvement of diaphragm.
6. Exclude involvement of portahepatis and SM vessels.

8. Surgical Technique for Peritonectomy: Six basic steps to be followed:

1. Proper exposure of abdomen parietal peritonectomy
2. Greater Omentectomy and Splenectomy if required.
3. Left upper quadrant peritonectomy
4. Right upper quadrant peritonectomy and capsule of liver and sub diaphragmatic space.
5. Lessor omentectomy, removal of omental bursa with cholecystectomy.
6. Pelvic peritonectomy the peritoneum below the pelvic brim including pouch of Douglus and bladder peritoneum.

9. Just before HIPEC - Check list to be verified

1. Securehaemostatis - most important
2. Complete cytoreduction(CC score)
3. Vitals stability
4. Drug dose as per BSA or NS/L
5. Placement of inflow outflow catheter and temp probe. Inflow catheter should be away from anastomotic site/sites.
6. Drug to be delivered only when inflow outflow temp would be in between 41- 43 C.

10. Mechanisms for HIPEC: Six mechanisms of Action of HIPEC [5]

1. Heat increases chemo drugs penetration into tissue up to 5-7 mm.
2. Heat itself has anti tumour effects and it increases cyto-toxicity.
3. Intra operative drugs and heat (41-42C) distributed manually to all surfaces in abdominal cavity.
4. Plasma peritoneal barrier limits systemic absorption of drugs and thereby less systemic adverse effect
5. Hyperthermia increases platinum sensitivity.
6. The time elapses during HIPEC (30-90 minutes) allows removal of small cancer nodules from surfaces including bowel serosa and mesentery.

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11. Morbidity and Mortality: Six common morbidities

1. Paralytic ileus with nausea vomiting - most common
2. Lymphocele formation
3. Anastomotic leak
4. Surgical site infection with wound dehiscence
5. Derangement of Renal function and RT I
6. Entero-cutaneous fistula(Mortality worldwide 0-10%)

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