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EDITORIAL

ANGELINA JOLIE EFFECT

Angelina Jolie, a celebrity and an actress published an essay in the New York Times about her decision in 2013 to get a double mastectomy. She never had breast cancer but she had inherited a "faulty" BRCA1 gene that increased her risk of developing breast and ovarian cancer. Jolie wrote "Today it is possible to find through blood test whether you are susceptible to breast and ovarian cancer and then take action." In 2015, she had her ovaries removed for the same reason. Thousands of women got tested for mutation in the breast cancer risk genes in the US but probably not the right women. People, who did not need to get the test, got the test. All that testing came at a cost. It was estimated that 4500 additional genetic tests were performed at a cost of $13.5 million.

Only a fraction of breast cancers result from an inherited gene mutation. But the Jolie essay had a profound effect on public suggesting medical professionals pay attention when celebrities talk about their own health. The message was loud and clear that celebrity endorsement can be extremely effective and relatively low cost compared to a lot of public health awareness campaigns.

Having a fault in BRCA1, mean that a woman carries between 40% to 85% risk of developing breast cancer and 40% to 60% risk of ovarian cancer. Currently, the guidelines do recommend genetic testing for women under 40 with a diagnosis of cancer. Bur breast testing is not recommended for anyone until age 18, at the earliest.

The dangers of carrying an abnormal BRCA gene are well documented. About 55% to 65% of women with harmful BRCA1 mutations are above 45% of BRCA2 women will be diagnosed with breast cancer by age 70, according to NCI. By some estimates, 39% of women who inherit a BRCA1 mutation and 11% to 17% who have an abnormal BRCA2 gene will develop ovarian cancer by age 70. Ovarian cancer occurs in above 1.3% of women in general population. Honestly, when patients are given their diagnosis, the first word in their mouth is "what about my daughter? What should I do to them? It makes them sad as mother.

For doctors, it is important to know who should be tested of BRCA mutation. How should the patient be counseled once they are test positive for BRCA mutations. Clinical decision – making selection of cancer risk reduction strategy (ie, surveillance, risk –reducing surgery, and / or chemoprevention) involve a trade off between life expectancy and quality of life. It is suggested that an average 30 year old women with BRCA mutation would gain from three to five years of life expectancy from prophylactic mastectomy and from 0.3 to 2 years of life expectancy from risk reducing oophorectomy. Gain in life expectancy declines with age at the time of risk reducing surgery and are minimal for 60 years old women. However, risk reducing surgery does not completely eliminate the risk of developing cancer as residual risks remain after mastectomy and oophorectomy. While prophylactic surgery is effective in cancer risk reduction, women should be counseled preoperatively about the potential morbidity of such procedures, and the possibility that surgery may affect libido, sexual functioning, and body image. Oophorectomy in premenopausal women can be associated with increased risks for bone and heart disease, and raises concerns about how to optimally manage surgical menopause and hormone therapy. Hysterectomy is not routinely recommended at the time of BSO unless other indications for this procedure exist. Moreover, there are no guidelines that recommend routine hysterectomy in BRCA mutation carriers.

For patients with BRCA mutation who do not wish to pursue surgical risk reduction, breast cancer surveillance should be offered and ovarian cancer screening may be performed. Patients with BRCA mutations should be educated regarding signs and symptoms of breast and ovarian cancer as appropriate. The screening starts at the age 18. Self breast examination performed periodically may facilitate awareness of changes, and clinical breast examination should be performed every 06 to 12 months beginning at age 25. Mammography should begin at age 30 or be individualized if the earliest age of onset in the family is under age 25. However, the sensitivity of mammography for detecting breast cancer in mutation carriers appears to be lower than in other high – risk women. MRI for breast cancer screening is recommended annually beginning at age 25 and can be scheduled six months after annual mammogram. Ovarian cancer screening with concurrent transvaginal ultrasound (preferably day 1 to 10 of menstrual cycle) and CA – 125 (best performed after day 5 of menstrual cycle) every six months beginning at age 30 or 5 to 10 years before the earliest age of first diagnosis of ovarian cancer in the family.

Chemopreventive strategies to reduce the risk of breast cancer have focused exclusively on prevention in high – risk women and involve the use of selective estrogen receptor modulators (SERMs) and aromatase inhibitors. Tamoxifen reduces breast cancer risk by 62% in BRCA2 carriers (relative risk {RR}0.38) but not in BRCA1 carriers (RR 1.67).

Pop culture icons can influence our fashion choices, dietary habits and brand preferences, but can celebrities also influence our medical decisions? The answer is a resounding yes. While there are clear benefits in genetic testing but they could also create anxiety and compel patients and clinicians to perform further testing or undergo premature or unnecessary clinical interventions. Testing and treatment decisions should be made on case to case basis. Surgery worked for Angelina Jolie, but certain nonsurgical options might be a better fit for some women. There's no right or wrong answer to whether a patient should get a genetic test, it's important to get a full understanding of the situation to make a well – informed decision.

Dr. A. K. Dewan
Director - Surgical Oncology

LUNG CANCER TARGET THERAPY – DAWN OF THE NEW ERA

If there is one disease that has plagued the human race for centuries, captured the imaginations of writers and cinematographers, and to an extent, "foxed" doctors, clinicians and scientists — it has to be cancer. This is an unending fight but with a ray of hope in the horizon. In this column I will discuss the latest treatments apart from chemotherapy available for stage 4 lung cancer.

According to GLOBOCAN 2012 database approx 53728 numbers of patients were diagnosed with lung cancer of which 48697 patients succumbed to their illness. This might in fact be an understatement in light of poor reporting and lack of good imaging and pathology services in different part of this world, one of the most exciting developments in lung cancer medicine is the introduction of targeted treatments. Unlike chemotherapy drugs, which cannot tell the difference between normal cells and cancer cells, targeted therapies are designed specifically to attack cancer cells by attaching to or blocking targets that appear on the surfaces of those cells. More than 50% of people in India suffering from non small cell lung cancer have some type of targetable mutations. People who have advanced lung cancer with certain targetable mutations on their tumor cells may receive treatment with a targeted drug alone or in combination with chemotherapy. These treatments for lung cancer include:

Oral tyrosine kinase receptor inhibitors: The epidermal growth factor receptor (EGFR) act as doorways by allowing substances inside the cell which encourage a cancer cell to grow spread and immortalize. A number of oral targeted treatments like erlotinib, gefitinib and afatinib have been shown to benefit some people with non-small cell lung cancer. Lung cancer cells that have a mutation on the EGFR are likely to respond with tyrosine kinase inhibitors.

ALK inhibitors: EML-ALK mutations when present in the cancer cell make the cancer more deadly. But at the same time EML-ALK mutation if present in a cancer cells gives the patient a chance to be treated with some of the oral ALK inhibitor like Crizotinib, and Ceretinib.

Other types of targetable mutations (although rare) against which targeted treatment is available are Met Amplification, ROS rearrangement and HER 2 amplification inhibitor of angiogenesis. Just like normal tissues, tumors need a blood supply to survive. Blood vessels grow in several ways. One way is through the presence of a substance called vascular endothelial growth factor (VEGF). This substance stimulates blood vessels to penetrate tumors and supply oxygen, minerals, and other nutrients to feed the tumor. When tumors spread throughout the body, they release VEGF to create new blood vessels.

Bevacizumab works by stopping VEGF from stimulating the growth of new blood vessels. (Because normal tissues have an established blood supply, they are not affected by the drug.) When combined with chemotherapy, bevacizumab has been shown to improve survival in people with certain types of non-small lung cancer, such as adenocarcinoma and large cell carcinoma.

Immunotherapy

Immunotherapy has recently emerged as a new treatment option for certain lung cancers. While any cancer treatment can cause side effects, immunotherapy is generally well-tolerated; this is in part due to its mechanism of action.

Our immune system is constantly working to keep us healthy. It recognizes and fights against danger, such as infections, viruses, and growing cancer cells. In general terms, immunotherapy uses our own immune system as a treatment against cancer.

In March 2015, the FDA approved the immunotherapy nivolumab (Opdivo) for the treatment of metastatic NSCLC which was unsuccessfully treated with chemotherapy. Nivolumab works by interfering with a molecular "brake" known as PD-1 that prevents the body's immune system from attacking tumors.

The other drug with the same mechanism of action called pembrolizumab (Keytruda) was later approved in Oct 2015 by FDA for the same indication.

Additional approaches to immunotherapy for lung cancer have shown promise in early clinical trials and are now in late-phase development. Treatments for NSCLC have advanced the furthest; however, a number of new immune-based treatments for SCLC are also in clinical development. These treatments fall into four main categories:

- Monoclonal antibodies are lab-generated molecules that target specific tumor antigens (a substance that the immune system sees as being foreign or dangerous)
- Checkpoint inhibitors target molecules that serve as checks and balances in the regulation of immune responses
- Therapeutic vaccines target shared or tumor-specific antigens
- Adoptive T-cell transfer is an approach in which T-cells (a type of white blood cell) are removed from the patient, genetically modified or treated with chemicals to enhance their activity, and re-introduced into the patient with the goal of improving the immune system's anticancer response

With advent of targeted agents and many new molecules in pipeline, the landscape of lung cancer treatment and prognosis is due for radical change.

Dr. Ullas Batra, Sr. Consultant & Chief of Thoracic Medical Oncology
Dr. Mohit Agarwal, Consultant – Head & Neck, Gastrointestinal Medical Oncology

HYPERTHERMIC INTRAVESICAL CHEMOTHERAPY FOR NON MUSCLE INVASIVE URINARY BLADDER CANCER: A PROMISING THERAPY

Introduction

Urinary bladder cancer is the ninth most common cancer and the most common cancer of urinary tract. According to WHO 4,30,000 new cases of urinary bladder were diagnosed in 2012. In the United States, approximately 79,000 new cases and 17,000 deaths occur each year due to bladder cancer. More than 90% of bladder cancer are urothelial or transitional cell carcinoma. Approximately, 70% of urothelial cancer are superficial or non-muscle invasive cancer. Among these non-invasive cancers, diseases can range from low grade that behave in very indolent manner to more aggressive high grade lesion. These high-grade lesions have high incidence of recurrence rate (50 – 70%), and progression rate (20 - 30%).

Cytotoxic intravesical chemotherapy or immunotherapy is recommended for non muscle invasive urinary bladder cancer after transurethral resection of bladder tumor (TURBT) to reduce recurrence and progression rate. Inspite of intravesical therapy, roughly 50% patients still experience a recurrence within 5 year. Several new methods like Chemo-thermotherapy (C-HT) or Hyperthermic intravesical chemotherapy (HIVEC) have been investigated to decrease the rate of recurrence and complication of intravesical therapy with very promising results.

Thermo Chemotherapy

Due to extensive global experience with its use and a significant amount of preclinical data demonstrating improved antineoplastic efficacy with heated mitomycin C. Mitomycin is the most common intravesical chemotherapy agent used in conjunction with hyperthermia (HT). There are several potential reasons for improved MMC efficacy when combined with heat. One explanation is that heat increases the penetration of MMC into the urothelium due to increased cellular membrane permeability and / or modified blood perfusion. HT is also directly cytotoxic and is known to alter intracellular metabolism, to damage DNA, to impair cellular proliferation, and to increase tumor cell apoptosis. Lastly, HT has been shown to increase the cytotoxicity of MMC, making the drug itself more effective.

The most common form of C-HT uses the Synergo HT system, in which local HT is administered via direct microwave irradiation of the urothelium by means of a 915-MHz intravesical microwave applicator. The target intravesical temperature is set between 410C and 440C and is measured by five thermocouples integrated in a 20-F treatment catheter. To avoid injury, the urethra is continuously cooled. Combat HIVEC™ is another device to deliver C-HT which is popular and available in our hospital.

Role of C-HT has been evaluated in various settings. It has been used for bladder cancer before resection of tumor, after resection of tumor, and after failure of previous intravesical therapy. Role of C-HT has also been studied in bladder preservation protocols', where patients are not fit for radical cystectomy or they do not want radical cystectomy. Approximately, 62.5% patients show a complete response with use of C-HT in neoadjuvant setting. The cumulative incidence of recurrence after 2 and 4 year is 12.5% and 20.8% respectively.

Comparative studies between efficacy of MMC alone and C-HT using MMC have established superiority of C-HT. The recurrence rate after MMC alone is several-fold higher than that of C-HT (17.1% vs 57.5%). C-HT is also used in patients of previous failed intravesical therapy. Patients who failed on previous intravesical MMC therapy respond very well but, patients of BCG failure are not very good candidates for C-HT.

Combat BRS HIVEC Ricirculator

C-HT is associated with several adverse events like bladder spasm, bladder pain, frequency, urgency. Though frequency of side effects in C-HT is slightly higher in comparison to MMC therapy alone, but it is not significantly higher. These side effects can be managed easily with pain killers and anticholinergics.

Conclusion

Hyperthermic chemotherapy has already been proved effective in intraperitoneal malignancies like ovarian and gastrointestinal cancers. Similarly, HIVEC was investigated and found efficacious in reducing recurrence and progression rate of bladder cancer. Incidence of adverse effect of any new therapy is main hurdle for its success, and fortunately side effects of HIVEC are not significantly higher. Several international guidelines like, NICE, EAU, and AUA have also included HIVEC as a treatment option for superficial bladder cancer based on robust results of HIVEC.

Dr. Amitabh Singh
Consultant – Surgical Oncology

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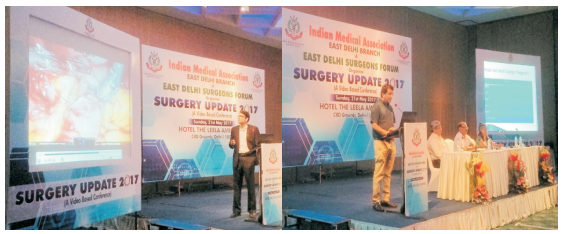
CME ON ABLATIVE THERAPIES

The Department of Radiology at RGCIRC organized a CME on Ablative Therapies on Friday, 19th May 2017 at Hotel Crowne Plaza, Rohini, Delhi. The CME had scientific lectures on Tumor Ablation: Planning Technology, Radiofrequency Ablation, Microwave Ablation, Ablations beyond the Liver along with a panel discussion on "Optimizing Cases for Ablation". Various radiologists from across the country participated in the CME.

SURGERY UPDATE 2017

RGCIRC participated in the Annual Conference "Surgery Update 2017" of IMA East Delhi & East Delhi Surgical Forum held on Sunday, 21st May 2017 at Hotel Leela Ambiance, Karkarduma, Delhi. Dr. Sajjan Rajpurohit, Consultant – Medical Oncology delivered a lecture on "Advances in Head and Neck Oncology" & Dr. Amitabh Singh, Consultant – Surgical Oncology spoke on "Robotic Uro Oncology" in the same.



CME - IMA AYUSH, FARIDABAD

RGCIRC organized a CME in association with IMA Ayush, Faridabad on Saturday, 10th June 2017 at Hotel Abhinandan, Faridabad. Dr. Ullas Batra, Sr. Consultant and Chief of Thoracic Medical Oncology delivered a lecture on "Approach to Lung Cancer" and Dr. Leena Dadhwal, Consultant – Surgical Oncology spoke on "When to suspect Cancer" in the said CME.

WELCOME TO RGCIRC FAMILY - DR. MANISH PRUTHI

Dr. Manish Pruthi has joined as Consultant – Orthopedics Surgical Oncology. He is an alumnus from Maulana Azad Medical College (MAMC), Delhi. He earned his MS from PGIMER, Chandigarh and DNB from National Board of Examinations (NBE), New Delhi. He has a vast experience in surgical management of bone tumors and soft tissue sarcomas. He did his Diploma in Tissue Bank from National University of Singapore and fellowship in Bone and Soft Tissue Tumors from TMH, Mumbai.

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