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EDITORIAL

TRIBUTE TO DR. K K PANDEY BY HIS STUDENTS



Born in Pratap Garh, UP on May 18, 1937, Kamla Kant Pandey moved to KGMC, Lucknow for his graduation and post-graduation in surgery. He then joined as faculty member of Surgery Department at Maulana Azad Medical College. His students called him an exceptional and inspirational teacher. Over years he touched the lives of thousands of students, staff and patients.

Eminent surgical oncologist Dr. K. K. Pandey was avante-garde-witness to the beginning of Rajiv Gandhi Cancer Institute & Research Centre. He came from Safdarjung Hospital with rich oncology experience and joined as “The cancer man” a surgeon with a formidable reputation preceding him. He was the first one to spearhead the concept of Tumor Board in Pvt. Sector. He preached what he did and said” A

clinician must have clarity, gravity and dignity.” The foremost concern when a patient came to him was “what is the best I can do for him. No one is perfect but remember you give your utmost.” Dr. Pandey playfully tweeted the intellectual ears of the younger lot with degrees that don't make a man; experience does.

He was often criticized for something or the other. I believe it takes character not to be disheartened by critics. Critics always sit at the sidelines. They are underachievers they are not the leaders but they shout at doers. The critic is one who knows the price of everything and the value of nothing. I remember him saying “Relationships don't last because of passion and love but because of commitment and empathy. A commitment implies putting the other person's needs ahead of one's own”.

We cannot forget the Darbar at RGCIRC. Dr. K. K. Pandey talked of words of wisdom, and quotes from Gita and Puran. We are catching up with knowledge from literature but we will miss the pearls of his wisdom. Life is not about the steps you have taken but the footprints you have left behind.

He always preached

1. “Come from an institution, not from a place
Come from a teacher, not from a book”
2. There is no final line in the race of excellence.
3. All surgeons are in the cabin of a flight. Machine is the same; patient is same; training is same but the art is different.
4. My patient should not die of my surgery. If he has to die, let him die of his disease.

In his book “Blessings of Guru” dedicated to his Guru, Dr. Pandey had talked about personality of a good doctor, ethical issues in medical profession and life after death. He called compassionate care as spiritual care of patient which involves “serving the whole person”. Cure is not possible for many cancers but he firmly believed that there is a room for healing. Healing could be experienced as acceptance of illness and peace with one's life. This healing is spiritual. Patients come to doctors to seek care for their medical condition. In delivering this care, doctor should be respectful and understand the spiritual dimension in patient's life.

The legacy that Dr. Pandey has left will not be forgotten; we at RGCIRC will continue to serve each year through combination of sophisticated equipments, technology and straight from the heart compassion. The philosophy of “high touch and high tech” founded by Dr. Pandey at RGCIRC will continue to grow.

May his soul rest in peace

Dr. Rajiv Kumar
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THE EGFR SAGA: MOLECULAR BASIS & OVERCOMING RESISTANCE

The discovery of epidermal growth factor receptor (EGFR) mutations in non small cell lung cancer (NSCLC) has allowed the identification of a subset of patients whose tumours are exquisitely sensitive to EGFR tyrosine kinase inhibitors (TKIs). Among patients with EGFR-mutant tumours, a 75% RR is observed, indicating that approximately 25% of cases do not respond to a TKI (compared with 90% of unselected patients with NSCLC). Despite the efficacy and superiority of EGFR TKIs over chemotherapy as first-line therapy, all patients will ultimately develop progressive disease, with a median of 9–13 months progression-free survival. A better understanding of the molecular mechanisms underlying resistance to EGFR TKIs can help design new drugs and therapeutic strategies to overcome resistance. This has been illustrated by the new generation TKIs that are effective on the T790M mutation, which is the most frequent mechanism of acquired resistance to EGFR TKIs. Hence it is prudent to understand molecular basis of both the primary and secondary resistance to EGFR TKI.

Definition of resistance

The study of resistance to EGFR TKIs in EGFR-mutant NSCLC patients can be divided into primary and acquired resistances, which have different origins. Primary resistance refers to patients who had progressive disease or stable disease as the best response to EGFR TKI, whereas acquired, or secondary, resistance refers to patients who had progressive disease following an initial objective response or prolonged stable disease. JACKMAN et al. [1] have proposed a detailed definition of acquired resistance to EGFR TKIs, which relies on: 1) the presence of a known activating EGFR mutation associated with sensitivity to EGFR TKI or a prolonged response or stable disease to EGFR TKI (>6 months); 2) treatment with an EGFR TKI as a monotherapy; 3) disease progression upon uninterrupted exposure to EGFR TKI; and 4) no additional systemic therapy since discontinuation of EGFR TKI. The occurrence of osteoblastic reactions during treatment with TKIs, while the primary tumour and metastases are stable or in response, should not be considered as disease progression [2].

Primary resistance to EGFR TKIs

Depending on the mutation present in EGFR, tumors exhibit differential TKI sensitivities. While the most common EGFR-activating mutations, L858R and exon 19 deletion, typically confer sensitivity to EGFR TKIs, other primary EGFR mutations can confer resistance. Exon 20 insertions or duplications, which account for approximately 4-9% of EGFR mutations, appear to be resistant to EGFR inhibitors in vivo. Other, much less frequent, primary EGFR mutations such as G719X and L861X, have been reported.

Although recognized mainly as a mechanism for AR, another EGFR exon 20 mutation, T790M, has also been associated with primary resistance. Minor clones with the T790M mutation have been identified in treatment-naïve tumors that contain classic sensitizing mutations. While this mutation has low allelic frequencies in treatment-naïve tumors, pressure from TKIs may select for enriched growth of these T790M clones, leading to overall AR.

Frequency of rare EGFR mutations and efficacy of EGFR TKIs

Rare mutations	Frequency among EGFR rare mutations %	ORR %	DCR %	PFS 26 months on EGFR TKI %
Exon 18 mutations	18	7	34	34
Exon 20 mutations	51	8	44	44
Complex exon 18 and exon 20 mutations	11	57	86	86

EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitors; ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival.

ACQUIRED RESISTANCE

Gatekeeper mutation in EGFR: T790M mutation

T790, located in the ATP binding pocket, is named “the gatekeeper residue” as it determines the affinity of ATP-competitive EGFR-TK inhibitors to EGFR-TK. Substitution of Threonine 790 with Methionine (T790M) increases the ATP's affinity to EGFR and attenuates the binding efficacy of gefitinib and erlotinib consequently [5]. Approximately 50% of the acquired resistance developed to erlotinib or gefitinib is linked to T790M mutation.

Compensatory contribution of other RTKs

c-MET

MET receptor, a trans-membrane tyrosine kinase encoded by proto-oncogene MET, has been highlighted as an important cause for acquired resistance of NSCLC to gefitinib or erlotinib.

IGF-1 Receptor

Growing evidences have emerged for the involvement of the IGF-1 Receptor (IGF-1R) pathway in the acquisition of resistance to EGFR-TKIs. Constitutive activation of IGF-1R pathway has been detected in multiple gefitinib or erlotinib resistant lung cancer lines.

HER2

HER2 mutation occurred at about 2% of patients with NSCLC, significantly more frequent in never smokers, adenocarcinoma histology, oriental ethnicity and female gender. Almost all HER2 mutations locate in exon 20, encoding the kinase domain of HER2 protein. NSCLC cells holding the mutant HER2 are more potent in activating downstream signal transducers and exert resistance to EGFR-TKIs and knockdown of the mutant HER2 succeed in restoring sensitivity to EGFR-TKIs.

Activation of compensatory signaling pathways

PI3K/AKT/mTOR signaling pathway



JAK2/STAT3 pathway

SCLC phenotypic transforming-No exact mechanism underlying this phenomenon has been launched. Probably, SCLC cells originate from the minor pre-existent cells under the selection pressure of EGFR-TKIs, or trans-differentiate from the adenocarcinoma cells, or arise from the multi-potent stem cells

Targeting EGFR T790M**Secondary generation EGFR-TKIs**

In view of the fact that resistant tumor cells are still addicted to the EGFR signaling pathway, new drugs which can irreversibly block EGFR-TK via the formation of covalent bonds in the pocket of the catalytic site should be able to increase the potency of EGFR-TK inhibition. One such inhibitor, the second generation EGFR-TKI afatinib (BIBW2992), designed to bind covalently with Cys-797 at the gatekeeper pocket, can potently and selectively block both wild-type and mutant forms of ErbB family receptors(7). The pooled analysis of those two large open-label phase III studies announced in the 2014 ASCO Annual Meeting proved the favorable anti-tumor activity of afatinib. Median OS was prolonged from 24.3 months in chemotherapy group to 27.3 months in the afatinib group (HR=0.81; CI 0.66 to 0.99; p=0.037).

Third generation of EGFR-TKIs

In view of this, the third generation EGFR-TKIs that selectively target the mutant EGFR, in particular the T790M mutation, but exhibiting minimal potency toward the wild-type receptor emerged in quick succession. CO-1686 is one of them and exhibits potent inhibition of EGFR T790M but circumvents wild-type EGFR

Osimertinib(8) (Tagrisso(™), AZD9291) is an oral, third-generation epidermal growth factor receptor tyrosine kinase inhibitor for the treatment of advanced non-small cell lung cancer (NSCLC). Osimertinib has been designed to target the EGFR T790M mutation that is often present in NSCLC patients with acquired EGFR TKI resistance, while sparing wild-type EGFR. In November 2015, the tablet formulation of osimertinib was granted accelerated approval in the USA for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC (as detected by an FDA-approved test) who have progressed on or after EGFR TKI therapy

Targeting HGF-MET pathway**Anti-HGF neutralizing antibody**

TAK-701 is a potent humanized monoclonal antibody to HGF. It works by suppressing the HGF binding to MET receptor and thus restrains the proliferation effects of MET pathway

MET tyrosine kinase inhibitors

Tivantinib is a non-ATP-competitive small molecule MET inhibitor. It works by stabilizing the inactive conformation of MET, and thus hinders the activation of downstream signaling pathway. Given the well-tolerance and potential ability of tivantinib both as single-agent therapy and in combination with erlotinib announced in several preclinical and phase I clinical trials, a series of work have and are being carried out to evaluate its antitumor efficacy

MET monoclonal antibody

Onartuzumab (MetMAB) is a newly developed humanized monoclonal antibody targeting MET. It blocks the HGF binding to MET, and thus attenuates the activation of its downstream transducers and effectors [9]. It was evaluated in a randomized phase II trial comparing erlotinib with and without onartuzumab in advanced NSCLC patients. Despite of no statistically significant differences between the two arms in the overall population, the combinational arm showed 47% reduction in the risk of disease progression and significant prolongation in median PFS (2.9 months versus 1.5 months; HR 0.53, 95% CI 0.283-0.99, p=0.04) and median OS (12.6 months versus 3.8 months; HR 0.37, 95% CI 0.19-0.72, p=0.002) in the subset of MET-positive, which was confirmed to be associated with bad prognosis

OTHER STRATEGIES UNDER TRIAL

Targeting HER3 pathway- combination of pertuzumab and erlotinib

Targeting PI3K/AKT/mTOR pathway

- 1.PI3K inhibitors-BAY 80-6946
2. mTORC1 inhibitors- Everolimus
3. Dual PI3K /mTORC1 /mTORC2 inhibitor
4. AKT inhibitors

Conclusions and perspectives

EGFR activating mutations have been overoptimistically recognized as the Achilles' heel of NSCLC after some clinical successes have been achieved. Unfortunately, almost all patients initially responding to gefitinib or erlotinib would inevitably progress to develop acquired resistance. To our relief, the constantly updating knowledge of the mechanisms underlying has already been translated to the development of novel targeted agents, rational combination regimens and improved survival benefits to NSCLC patients.

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**OSTEOSARCOMA UPDATE – 2016:
CONNECT, COLLABORATE, CONQUER.....**



Osteosarcoma Update 2016, organized by Rajiv Gandhi Cancer Institute and Research Centre on 12th and 13th November, was the first International conference ever in the country dedicated to osteosarcoma.

Eminent faculty from India and abroad shared their views on various aspects of management of this rare disease. It was attended by more than 125 doctors from across the country, including those from Mumbai, Bangalore, Pune, Chennai, Kolkata, Chandigarh, Varanasi, Ahmedabad and Rohtak apart from Delhi and NCR. The conference lasted for a day and a half and provided a very good platform for both the seniors and the beginners to interact and benefit from the others' experience and knowledge.

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Architect's Impression of RGCIRC (post expansion)



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