TKI and Its Effects on External Beam Radiation Therapy

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Growth factors are essential for the development of mammalian cells. Binding to the receptors of the cell surface, growth factors are essential for cellular communication underlying embryonic tissue embryonic tissue induction, fate determination, controlled cellular destruction, cell survival, tissue specialization, cell migration etc. Growth factors transduce extracellular signals through receptor translocation to the nucleus. Receptor Tyrosine Kinases (RTKs), Epidermal Growth Factor family of RTKs (ErbB) are one of the most studied receptors due to its role in development, physiology and cancer growth (The epidermal growth factor receptor family: Biology driving targeted therapeutics). Epidermal Growth Factor Receptor also belongs to the Receptor Tyrosine Kinases erbB2/HER-2, erbB3/HER-3, and erbB4/HER-4). These structures are situated in the cytoplasmic membrane of the cell and contain an extracellular ligand binding domain, transmembrane region and intracellular domain with tyrosine kinase function [1]. The normal expression levels of EGFR range from forty thousand to one-hundred thousand receptors per cell. NSCLC, Head and Neck, renal, ovarian, breast, and colon cancers have all been associated to overexpression of EGFR. Overexpression of EGFR leads to an enhanced signal generation and activation of downstream signaling pathways, ultimately resulting in uncontrolled cellular growth and invasiveness. There are multiple ligands that bind to and activate the EGFR. The most prominent being Transforming Growth Factor-α. The binding of a ligand to EGFR results in a conformation change of the cytoplasmic domain that stimulates tyrosine kinase activity. Phosphorylated tyrosine kinase residues arrange for the recruitment of signal transducers and activators of intracellular substrates such as Ras, which leads to an intracellular signal transduction cascade. The two main signaling pathways for EGFR are the Ras-Raf Mitogen-activated protein kinase (MAPK) pathway and the phosphatidyl inositol 3′ kinase and Protein Kinase B (Akt) pathway. These pathways are of particular interest to

researchers because they regulate a plethora of biological processes, such as gene expression, cellular augmentation, angiogenesis, and inhibition of apoptosis. Prior studies have shown that the EGFR pathway encourages tumor cell motility, metastasis, as well as adhesion [2].

The EGFR pathway becomes activated upon exposure to ionizing radiation, resulting in cellular proliferation. Fractionated radiation therapy leads to an increase in tumor copies, resulting in enhanced capabilities of the tumor cells to repair itself. The combination of rapid proliferation and enhanced DNA damage repair negates the toxic effect of radiotherapy. EGFR is an attracting molecular target because of its prominent roles in cellular proliferation, survival, and metastasis. Intervening in the activities of this target can lead to a disruption in the signal transduction pathway. Moreover, using drugs to inhibit this pathway can ameliorate radiation-induced apoptosis by preventing the tumor cells from entering G_2/M phase of the cell cycle [2].

The standard treatment of care for Non-Small-Cell Lung cancer is radiation therapy with concurrent chemotherapy. The use of a TKI had not been particularly studied and one phase II trial reviewed the role of a tyrosine kinase inhibitor with concurrent thoracic radiotherapy. Thirty-two patients that were selected for this trial had unresectable stage III NSCLC harboring EGFR mutations (exon 19 deletion, or exon 21 L858R point mutation, T_3N_1 stage cancer, and between the ages of twenty to seventy-four years. The methodology of this trial was utilizing 250mg/day of Gefitinib over the span of two years and receiving 64Gy of radiotherapy spread out over 32 fractions. Chest x-rays were taken every two months for the first months, then every six months. Brain MRIs were taken once a year. The results of this trial proved that molecular targets are becoming the new standard of care in NSCLC. Meanwhile, the efficacy of the molecular agents in conjunction with radiotherapy did not yield any significant results. The

authors of this study attributed that to the miniscule number of patients selected for this trial. This study also pioneered the utilization of Gefitinib with concurrent radiation therapy [3]

Another study aimed to investigate the role of conventional radiation therapy and stereotactic body radiation therapy in patients harboring the EGFR mutation. The study split the patients up into groups A, B, and C. Group A included patients who underwent RT no more than 30 days before the beginning of the TKI drug. Group B included those who underwent RT no more than 30 days after the definitive suspension of TKI therapy. Group C included those who underwent RT during the administration of TKI. The total number of patients that were used in the study was 50. Group A included 16 percent of the patients while groups B and C included 18 percent and 66 percent of patients, respectively. The median follow range was 16 months and was calculated from the start of the systemic therapy. The median overall survival was 19.3 months and the 1 and 2 year overall survival was71.5% and 36.5%, respectively. It was noted that SBRT was associated with a better overall survival. No other therapeutic modality significantly affected the overall survival. The outcomes of this trial indicates that RT combined with a TKI is a well-tolerated and shows promising results in terms of survival, particularly when stereotactic RT with ablative aim is applied and when RT is given concomitantly with TKI. Performing RT concomitantly and without suspension can prolong the duration of drug administration, possibly leading to a delay in the switch to a 2^{nd} line systemic therapy. RT can contribute to a better management of NSCLC with a driver mutation in a palliative way. Combining RT and systemic TKI therapy could provide major benefit and therefore must always be considered [4].

Chronic use of EGFR-TKI's can lead to an increase resistance often accompanied by a plethora of genetic alterations. Radiation has the capability to alter the DNA of tumor cells. This

can lead to radiation resistance. This kind of resistance can hybridize with TKI resistance, thereby affecting the TKI resistance mechanisms. Moreover, radiation can alter TKI resistance genes leading to an even more alteration of TKI resistance pathways. Studies have shown that radiation can decrease the rate of a particular mutation in EGFR, T790M. Leading to a decrease in the formation of TKI resistance. However, it has been shown that radiation can also induce the expression of transmembrane tyrosine kinase receptor proteins called c-MET. This is another important mechanism of TKI resistance. Consequently, this leads to an increase growth and proliferation of tumor cells under the influence of TKI's. The increasing use of radiotherapy combined with TKI's in NSCLC has led to an urgent need to study the impacts that radiation has on TKI resistance mechanisms. Extensive investigation is needed on the impact of radiation on TKI resistance pathways [5].

The most common side effects of EGFR-TKI's are diarrhea, acneiform skin rash, and paronychia. The less common side effects include mucositis, stomatitis, cornea erosion, and epistaxis. The severity and occurrence of the side effects are correlated with the potency of EGFR inhibition. Interstitial lung disease is idiosyncratic and typically not correlated with EGFR inhibitors. If a patient develops interstitial lung disease, TKI use is discontinued. Switching to a different type of TKI medication can resolve severe hepatic impairment. Other side effects can be resolved with a temporary dose interruption and further dose reduction [6].

Brain metastasis is found in approximately ten to twenty percent of patient's diagnosis with NSCLC. The overall survival rate with patients with brain metastasis are very poor with limited treatment options. Overall survival time of patients who did receive treatment is less than three months. Whole Brain radiation therapy (WBRT) is the standard of care for patients with brain metastasis stemming from NSCLC; with a median survival rate of three to six months.

Chemoradiotherapy yielded a median survival rate of seven point six to eight months. The tyrosine kinase inhibitor, Gefitinib, was documented to be effective with a median survival rate of nine to thirteen point five months. One study hypothesized that the disruption of the blood brain barrier by brain metastasis and radiation might further enhance Gefitinib to penetrate the blood brain barrier. Moreover, radio-sensitivity could be enhanced by Gefitinib. This was a retrospective study that mainly focused on comparing the efficacy of Gefitinib alone versus gefitinib plus concomitant WBRT. Ninety patients were selected in a time frame of four years. The participants had to be diagnosed with adenocarcinoma of the lung, confirmation of brain metastasis (measuring a minimum of 10mm in diameter) via MRI, and no treatment history of brain metastasis, with surgery, radiosurgery, EGFR-TKI or WBRT. The patients were prescribed 250mg of gefitinib until the radiological progressive disease, the dose of the WBRT was Forty-Gy over twenty fractions. In the test group, the interval of between the delivery of gefitinib to the beginning of whole brain radiation was fifteen days. The results of the study showed that Patients treated with gefitinib with concomitant WBRT had superior time to progression of brain metastasis compared with gefitinib alone group (10.6 vs. 6.57 months). The study also demonstrated a significant survival benefit of gefitinib with concomitant WBRT versus gefitinib alone (23.4 vs. 14.83 months). Gefitinib and concomitant WBRT showed an advantage over gefitinib alone in terms of progression free survival and overall survival of central nervous system lesions [7].

Another retrospective study assessed the efficacy of EGFR-TKI plus radiotherapy or TKI alone to treat NSCLC brain metastasis. Four-hundred and eighty-two patients were diagnoses with lung cancer with EGFR mutation between June of 2006 and December of 2015. One-hundred and eighty-one patients were enrolled from that pool with brain metastasis at the time of

diagnosis. All patients that developed brain metastasis after taking an EGFR-TKI as well as those who did not receive EGFR-TKI after SRS or WBRT were excluded. After diagnosis, all patients received either chemotherapy or a TKI as the primary form of systemic treatment. Ninety-six patients received TKI as the primary systemic treatment while the rest received TKI as a secondary systemic treatment. The patients all received EGFR-TKI oral treatments of icotinib (125mg/day), gefitinib (250mg qd), and erlotinib (150mg qd). The total dose of WBRT was 30Gy given over a period of 10 fractions. Ninety-one patients received radiotherapy before or concurrently with TKI. The rest of the ninety patients did not receive radiotherapy before TKI treatment. The patients underwent imaging examinations after two courses of chemotherapy or every 4 ±1 week for the first 2 months of EGFR-TKI treatment. Imaging examinations included chest, abdomen, and pelvic CT; they underwent brain MRI every 3 months until disease progression. In all 49 symptomatic BM patients, 45 received RT (39 WBRT and 6 SRS. The median OS was 21.1 months in WBRT and 37.1 months in SRS. In the group of asymptomatic patients, 86 did not receive brain radiation therapy before TKI (group A) and 46 received RT upfront or concurrently with TKI (group B). The PFS in group A and B was 9.6 months and 11.3 months, respectively. The median OS in group B was documented to be longer than group A, 24.9 months and 17.4 months, respectively. Further subgroups, among 74 patients, 33 underwent concurrent TKI and radiation treatment. Thirteen received TKI after 1st line failure of radiation therapy. The mOS of the three groups was 21.9 months, 26.2 months and 17.1 months, respectively. This study has concluded that patients that were treated with SRS can possibly improve the overall survival time for symptomatic BMs. On the other end of the spectrum, deferral of brain radiotherapy can result in an inferior overall survival in EGFR-mutated asymptomatic BMs [8]

In the treatment of NSCLC, it appears that targeted molecular therapy is becoming the new standard of care. Radiation treatments can be used in patients with driver mutations in a palliative way. More research needs to be done to determine if radiation can have an enhanced effect with a TKI in NSCLC patients. In the case of brain metastasis from NSCLC, the studies have shown that there is a survival benefit of patients taking a TKI with concomitant WBRT. The progression free survival and overall survival of the nervous system lesions increases in patients taking a TKI with concomitant WBRT versus a TKI alone. More research needs to be done in order to determine the efficacy of a TKI with radiation therapy. Many of the trials that have been done were retrospective and more clinical trials need to be done in order to get a more accurate determination of the effects that a TKI has on external beam radiation therapy.

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