Proceedings of The National Conference
On Undergraduate Research (NCUR) 2019
Kennesaw State University
Kennesaw, Georgia
April 11-13, 2019

The Efficiency of Targeted Therapy in Combination with Chemotherapy for Advanced ALK-Positive Lung Cancer in Non-Small Lung Cancer Patients: Proposing an Alternative Treatment

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Abstract

Patients who are positive for the anaplastic lymphoma kinase (ALK) mutation and are diagnosed for ALK-Positive Non-Small-Cell Lung Cancer (NSCLC) often have little to no response rates to first-line pemetrexed chemotherapy. A more effective way to treat this specific kind of lung cancer was developed using targeted therapy: crizotinib, a tyrosine kinase inhibitor (TKI). In multiple studies, crizotinib was shown to result in increased progression-free survival in patients when compared to pemetrexed. However, patients who suffer from ALK-Positive NSCLC often develop resistance to crizotinib within a year of treatment and are then treated with pemetrexed or a second-generation TKI, which are not as effective as crizotinib. This proposed study would combine crizotinib with pemetrexed as a first-line treatment of ALK-Positive NSCLC in order to increase the progression-free survival in patients. In this study, patients would receive an oral dose of crizotinib simultaneously with pemetrexed intravenous-chemotherapy, and the dosage and other specifics would be determined by the researcher. However, there are some challenges to this proposed treatment, mainly pertaining to the adverse events and the high cost of combining crizotinib and pemetrexed. Even though there are complications with the combination. it is still integral to test the effectiveness of this therapy. Due to promising results from other studies showing the positive effects of crizotinib, this study is suggested to try and improve the treatment of patients with ALK-Positive NSCLC. Although the percentage of the population who are positive for the ALK mutation is a small, ALK-Positive NSCLC still effects a lot of patients who suffer from the ALK mutation, causing them to not have a proper, effective treatment due to the resistance that develops. This paper focuses on an effort to find a more effective way of treating these patients and possibly increasing the response rates and increasing the overall progression-free survival, while limiting toxicity and cost.

Keywords: Crizotinib, Pemetrexed, ALK-Positive NSCLC

1. Introduction

Due to the countless amount of diseases that are driven by genetic mutations, pharmacogenomic information can be used to create personalized, or targeted medicine, to better treat patients. The Personalized Medicine Coalition (PMC) (2014) claimed that "dosing for drugs for things such as depression, anxiety, coronary artery disease, peripheral artery disease, inflammatory bowel disease, and cancer, has improved due to the genotyping of drug-metabolizing enzymes," and that a lot of patients have benefitted from personalized medicine, especially those with melanoma, leukemia, or metastatic cancers (specifically lung, breast, and brain).[10] Thus, targeted therapies when combined with genetic testing are often a new hope to cancer patients, since often times their genetic mutation renders then unresponsive to standard treatment.

Xalkori® (crizotinib), is a tyrosine kinase inhibitor used in treating non-small cell lung cancer (NSCLC) and is only effective for patients who are positive for the mutated anaplastic lymphoma kinase (ALK) gene. The ALK gene

encodes a transmembrane tyrosine kinase that is from the insulin receptor superfamily.[4] As indicated in the following picture, normally ALK activation is regulated by the ligand, which then in turn would regulate cell replication. However, for people who have the ALK-rearranged mutation, ALK is activated without the ligand, resulting in uncontrolled cell replication. Increased ALK activity caused by molecular mutations has been linked to several cancers, such as non-Hodgkin's lymphoma, rhabdomyosarcomas, renal cell carcinoma, thyroid cancer, neuroblastoma, and NSCLC.

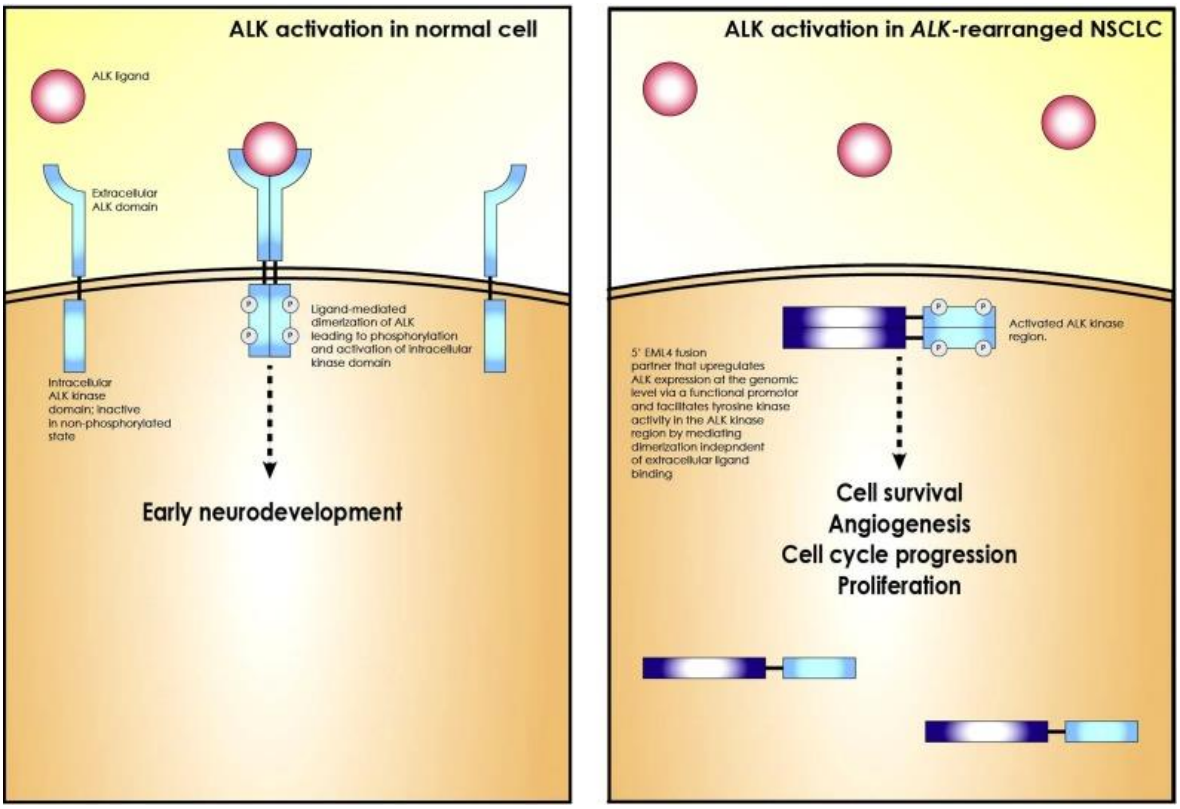

Figure 1. Biology of ALK-rearranged NSCLC.

ALK gene is rearranged or translocated in 2%-7% of NSCLC cases, causing a small percentage of NSCLC patients to have ALK positive NSCLC.[4] In ALK-activated NSCLC, the predominant molecular event leading to ALK is activated by the juxtaposition of the N-terminal portion of the protein encoded by the EML4 gene with the intracellular domain of the ALK tyrosine kinase.[7] This inversion is showed in the following figure, along with the downstream signaling pathways that lead to proliferation and cell survival, thereby leading to various forms of cancers.

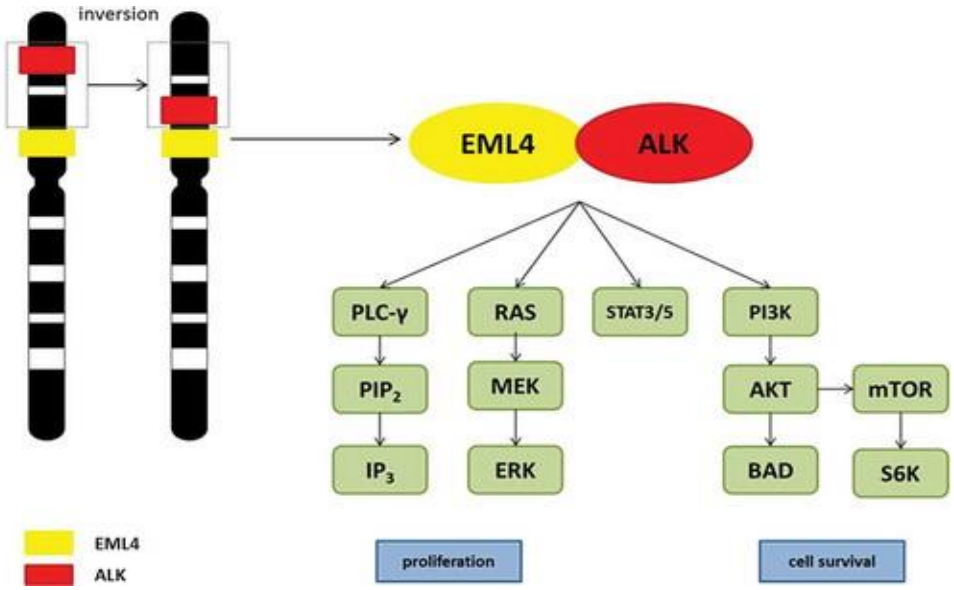

Figure 2. EML4-ALK fusion oncogene and downstream signaling pathways

In a first-line treatment setting, crizotinib was first to standard the normal platinum-pemetrexed chemotherapy and was almost equivalent to chemotherapy's successfulness in a second-line setting. It is tricky to treat this cancer, since most, if not all, patients treated with crizotinib develop a resistance to it, typically within 8 months.[8] Resistance develops either due to ALK-dominance (such as mechanisms that depend on ALK signaling), or ALK-non-dominance (such as mechanisms that are only partly or independent of ALK signaling).[7] Thus, patients are then reverted back to chemotherapy, which does not show the same number of response rates and the same length of progression-free survival in patients.

The big question is how ALK-positive NSCLC should be treated to maximize benefits, limit the toxicity and the cost, to ultimately increase the overall progression-free survival. Because patients with the ALK-Positive mutation who have ALK-Positive NSCLC are unresponsive to chemotherapy, show an increase in progression-free survival when treated with first-line crizotinib (targeted therapy) when compared to pemetrexed chemotherapy, and develop a resistance to crizotinib over time, a study where treating crizotinib in combination with pemetrexed may be more successful in increasing progression-free survival, than both therapies separately. There are some complications that could arise if this study were to happen, such as the high cost of using crizotinib, which would further increase with using pemetrexed, the toxicity from the two therapies combined resulting in adverse events, and the possible resistance that could develop.

2. Combining Crizotinib with Pemetrexed

According to Shaw et al. (2013), crizotinib was shown to be more successful in increasing the progression-free survival, increasing response rates, slowing the progression of cancer, reducing symptoms, and improving the quality of life of patients significantly when compared to second-line chemotherapy. Patients with the ALK-positive NSCLC are unresponsive to normal chemotherapy and are often treated in the order of chemotherapy, crizotinib, then chemotherapy again. In "Crizotinib Versus Chemotherapy in Advanced ALK-Positive Lung Cancer," Shaw et al. (2013) conducted a study in which they treated patients diagnosed with ALK-positive lung cancer with either basic chemotherapy or a gene-specific drug crizotinib, not simultaneously in patients who were previously treated after one prior platinum-based chemotherapy regimen.[12] The median progression-free survival, was 7.7 months with a 95% confidence interval (CI) from 6.0 to 8.8 months in the crizotinib group, as compared with 3.0 months with a 95% CI from 2.6 to 4.3 months in the chemotherapy group (p. 2389).[12] The found hazard ratio for disease progression or death with crizotinib was 0.49 (with a 95% CI, 0.37 to 0.64; $P<0.001$), while pemetrexed's hazard ratio for disease progression or death was 0.59 (with a 95% CI, 0.43 to 0.80; $P<0.001$) (p. 2389).[12] It was that concluded that according

to baseline characteristics and stratification factors, progression-free survival was longer with crizotinib than with chemotherapy.[12]

Likewise, in "First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer," Solomon et al. (2014) also conducted a study where patients were treated with either 250 mg of oral crizotinib twice daily, or received pemetrexed intravenous chemotherapy at 500 mg per square meter of body-surface area, (in addition to either cisplatin given at 75 mg per square meter, or carboplatin given with respect to the target area of 5 to 6 mg per milliliter per minute) every 3 weeks for up to six cycles (p. 2168).[13] It was found that progression-free survival was significantly longer with crizotinib than with the various chemotherapies, like Shaw et al. (2013), it was found that crizotinib had a longer progression-free survival of 10.9 months when compared to chemotherapy, which was 7 months (p. 2169).[13] The hazard ratio for progression or death with crizotinib was 0.45 with a 95% CI, from 0.35 to 0.60; P<0.001) (p. 2170).[13] The probability of 1-year survival was 84% with crizotinib and 79% with chemotherapy, and that objective response rates were 74% and 45%, respectively (P<0.001) (p. 2171).[13] Thus, it was concluded that crizotinib was superior to standard first-line pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced ALK-positive NSCLC (p. 2176).[13]

In further support, Chen et al. (2014), claimed that crizotinib is superior to standard chemotherapy in ALK inhibitor-naïve disease in "Co-Clinical Trials Demonstrate Superiority of Crizotinib to Chemotherapy in ALK-Rearranged Non–Small Cell Lung Cancer and Predict Strategies to Overcome Resistance." Mice were assigned to 3 randomized groups that were treated with crizotinib, pemetrexed, or docetaxel, and observed tumor regression at the dose of 100 mg/kg/d in the majority of animals, in addition to a high rate of partial response (68%; defined as >30% tumor regression) or stable disease (23%).[1] It was concluded that, "These results indicate that the response of ALK-driven tumors to crizotinib may be dose-dependent and suggest that insufficient ALK inhibition may be one of the mechanisms for primary crizotinib resistance observed clinically.[1] Notably, even at 100 mg/kg/day, very few mice (2/22) achieved near-complete remission (>90% tumor regression). Also of note, 2 of 22 mice exhibited primary resistance" (p. 1206). Additionally, the objective response rate to crizotinib was significantly higher than pemetrexed or docetaxel.[1] It is suggested that combining ALK and Heat Shock Protein 90 (HSP90) inhibitors may also be promising and found that the application of crizotinib and 17-DMAG in rapid succession greatly decreased FDG-PET activity in tumors driven by native EML4-ALK.[1]

These three aforementioned researchers used different techniques in their work: Shaw et al. (2013) conducted their study on patients who were mostly younger than 65 years of age, had never smoked and had adenocarcinoma of the lung with metastatic ALK-positive lung cancer, Solomon et al. (2014) compared crizotinib to pemetrexed-plus-platinum chemotherapy in patients, instead of just pemetrexed, and Chen et al. (2014) looked at tumor regression in mice.[1] Even though these three vastly different methods were used, they all came to a consensus: crizotinib superior to pemetrexed.[1,12,13]

However, in "Overcoming Crizotinib Resistance in ALK-Rearranged NSCLC with the Second-Generation ALK-Inhibitor Ceritinib," Most, if not all, patients developed a resistance to crizotinib within 8 months (p.147).[8] Patients develop resistance to crizotinib, either due to ALK-dominance (such as mechanisms that depend on ALK signaling), or ALK-non-dominance (such as mechanisms that are only partly or independent of ALK signaling).[7] The drug resistance from standard chemotherapy is non-existent/has not been observed in patients thus far. In order to combat the resistance from crizotinib while maintaining the positive outcomes, such as improved response rate and progression-free survival, standard chemotherapy can be used simultaneously with crizotinib. However, there is no evidence to prove that simultaneous usage of the aforementioned medications will not result in a drug resistance. There are second generation ALK-inhibitors, are certinib and alectinib, that can be implemented in treating patients when they develop a resistance to crizotinib, a first-generation ALK-inhibitor.[7] There are also other alternative treatment strategies to overcome resistance to crizotinib, such as HSP90 (a heat shock protein), and immunotherapy.[7]

Because of this, treating patients with crizotinib and pemetrexed simultaneously as a first line treatment could possibly be a better alternative to using either crizotinib or pemetrexed as a first line treatment, resulting in a higher progression-free survival of patients.

3. Cost/Benefit Analysis of Using Crizotinib and Pemetrexed

Even though treating patients with crizotinib may not be cost effective due to the high cost of drugs, and the low number of people in the population who have the specific biomarker of EML4-ALK fusion, combining crizotinib and pemetrexed should not be overlooked, and instead should be looked more into as a possible life-saving treatment.

In "Cost-Effectiveness of EML4-ALK Fusion Testing and First-Line Crizotinib Treatment for Patients with Advanced ALK-Positive Non–Small-Cell Lung Cancer," Djalalov et al. (2014) used a Markov model to analyze the cost-effectiveness of targeted therapy in addition to crizotinib. It was projected that first-line crizotinib gives 0.64 years (7.7 months) extra survival, or 0.38 quality-adjusted-life-years (QALYs), at an additional cost of $95,000 compared with standard of care, leading to incremental cost-effectiveness ratio (ICER) of $148,000 per additional life year, or $250,000/QALY gained.[3] Hence, it was concluded that that testing for EML4-ALK fusion while using crizotinib may not be cost effective.[3] Even though it is not cost effective, testing for EML4-ALK fusion is still important since a part of the population could be eligible for EML4-ALK fusion testing, albeit a small amount.

In "Cost-Effectiveness of Crizotinib for Anaplastic Lymphoma Kinase–Positive, Non–Small-Cell Lung Cancer: Who Is Going to Blink at the Cost?" Kelly, Hillner, and Smith (2014). (2014) agreed with the aforementioned model that first-line crizotinib gives 0.64 years (7.7 extra survival, or 0.38 QALYs, at an additional cost of $95,000 compared with standard of care, leading to ICERs of $148,000 per additional life year, or $250,000/QALY gained.[3,5] Further proving the subject matter, it was questioned if it is affordable to screen everyone with lung cancer for the ALK rearrangement if only 3% to 5% of the population will be ALK-positive, and if crizotinib is an affordable drug.[5] Kelly et. al (2014) focused on screening patients with advanced NSCLC but confined to adenocarcinoma, adenocarcinoma in never-smokers, and adenocarcinoma in never-smokers, who had the wild-type epidermal growth factor receptor and KRAS. These types of patients showed increased the frequency of ALK positivity to approximately 3.7%, 13.7%, and 35.9%, respectively.[5] At a drug price of $9,600/month, even if the frequency of ALK-positive patients is more than 50%, the cost-effectiveness is still more than $100,000/QALY; if the frequency is 1%, then the drug price needs to be lowered to less than $2,300/month to meet recognized cost-effectiveness criteria.[5]

However, since the completion of the Human Genome Project (HGP) ten years ago, there has been more than a 16,000-fold decrease in gene sequencing costs, which should reflect in lower drug prices, regardless of the frequency of ALK-Positive NSCLC patients.[10]

In "Cost-Effectiveness of Pemetrexed for Previously Treated Advanced Non-Small Cell Lung Cancer," Pavlakis et al. (2016) used a phase III clinical trial comparing pemetrexed and docetaxel and calculated the incremental cost ratio (ICER) to determine whether pemetrexed or docetaxel was more cost effective in patients who have been previously treated for advanced NSCLC (p. 6084).[9] The cost-effectiveness of pemetrexed was determined by evaluating the decrease in toxicity-related hospital admissions, and found that out of 571 patients, toxicity-related hospital admissions were 7.1 admissions per 100 patients for pemetrexed and 24.3 admissions per 100 patients for docetaxel and used that to evaluate the ICER (p. 6084).[9] As a result, patients who received prior treatment, pemetrexed is cost effective, and that pemetrexed also minimizes toxicity-induced hospitalization, without compromising efficiency of the therapy since the incremental cost for pemetrexed includes considerable savings in toxicity management, and that the ICER to avoid an additional toxicity-related hospitalization was $20,460 in Australian currency (one Australian dollar is equivalent to 77 cents in the US), which amounts to $15,755 USD (p. 6084).[9]

Even though multiple aforementioned cost/benefit analyses of crizotinib claimed that it was not economically feasible, due to the high cost of drugs, and the low number of people in the population who have the specific biomarker of EML4-ALK fusion, the usage of crizotinib as a treatment should not be overlooked. Treating patients with crizotinib may not be cost effective, but in terms of payoff, a therapy that could have a better chance of increasing response rates and progression-free survival may be worth the high cost. The alternative suggested treatment of using crizotinib with pemetrexed could be beneficial to the quality of life of the patient, especially since pemetrexed is deemed cost effective.[9] Yes, the cost may be high to combine both crizotinib and pemetrexed, but it may be worth it if the treatment is going to increase the progression-free survival.

4. Adverse Events Involved with Therapy

Even though there could be severe grade 2 level toxicity induced adverse events (moderate symptoms that may need minimal, local or noninvasive intervention) when combining crizotinib and pemetrexed such as hepatic, pulmonary, hematologic, renal, endocrine, and fertility disturbances, in addition to nausea and diarrhea, treatment should still be explored because it could be a life-saving treatment that outweighs the adverse events.

Patients experienced grade 1 (asymptomatic or mild symptoms that most likely not need any intervention) to grade 2 toxic effects when treated with both crizotinib and pemetrexed.[12] Likewise, Dikopf, Dr. Kevin Wood and Dr. Ravi Salgia, the recipient of the IACA Award for Outstanding Contributions to Oncology, stated that the most common adverse effects of crizotinib were nausea (56.9%), diarrhea (48.6%) and vomiting (45.5%), and overall, less than 1% of these effects are grade 3 or 4 (p. 487). In "First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung

Cancer," Solomon et al. (2014) agreed with Dikopf et al. (2015) that the most adverse events were nausea and diarrhea.[13] (p. 2167) However, edema and vision disorders were very common in his study (p. 2172).[13] The most common adverse events of crizotinib include cardiac and endocrine abnormalities, ocular and gastrointestinal disturbances, and peripheral edema (28%).[2] It was also stated that grade 3 (disabling severe symptoms that are medically significant but not immediately life-threatening that need some form of hospitalization or prolongation of hospitalization) or grade 4 (life-threatening symptoms that require urgent intervention) neutropenia and lymphopenia occurred in 12 and 9% of crizotinib-treated patients, respectively, and that one patient suffered from febrile neutropenia (p. 487).[2] Patients suffered from hepatic disturbances, due to drug-induced Elevations of alanine aminotransferase (ALT) > 5 times the upper limit of normal occurred in 109 patients (p. 490).[2] Many patients suffered from pulmonary disturbances within the first two months of therapy, since out of 1225 patients across multiple clinical trials, 2.5% of patients developed interstitial lung disease (ILD)/pneumonitis (any grade), 11 patients (0.9%) had grade 3 or 4, and 6 patients (0.5%) had fatal cases.[2] In further support, Pistone, Durieux, Grigoriu, and Meert (2018) stated that they "…found 12 case reports of ILD in the intensive care unit (ICU), all caused by crizotinib. In the 12 published case reports, 4 of these patients died and 8 had a partial or complete resolution of their pulmonary involvement. Créquit et al showed an overall incidence of 20.7% (any grade) and 7% for ≥3 grade.[11] Two types of crizotinib-associated ILD are described. The first occurs rapidly after treatment initiation is severe, irreversible, and fatal in most of the cases even if crizotinib is stopped" (p. 6). There were also dermatologic disturbances found in 9-11% of patients who reported rashes (p. 490).2 Additionally, 7% of patients experienced renal disturbances and developed renal cysts with crizotinib, while only 1% of patients did with chemotherapy, and other adverse events were fertility and hypogonadism (p. 489).[2] Around 5% of patients who were treated with crizotinib demonstrated potential profound bradycardia, which is characterized by less than 45 beats per minute (p. 488).[2] These side effects were mostly grade 1 or 2, and were reported in 97% of patients, and lot of these side effects were due to the multiple tyrosine kinases inhibited by crizotinib and will likely improve with second and third-generation inhibitors that inhibit ALK more specifically (p. 487).[2] Of these adverse effects, the most commonly described effect was visual disturbances, shown in approximately 62% of cases (p. 487).[2] These visual disturbances typically occurred when ambient lighting changed from dark to light, and patients would report seeing trailing or flashing lights on moving objects; these disturbances usually occurred near the beginning of therapy, often within the initial 2 weeks of treatment.[2] The patients reported that the visual disturbances were not bothersome to them, and minimally impacted their quality of life, since these visual disturbances usually only lasted up to 60 seconds, in return, the dosage of crizotinib did not have to be changed for most patients, however 15% of patients did require a dose reduction.[2] Interestingly, it was noted that Asian patient had higher rates of adverse events, however it could be due to the higher maximum concentration found in Asian patients during the initial assessment of crizotinib pharmacokinetics (p. 486).[2] Even though grade 3 or 4 adverse events were rare, they were more common in non-Asian patients.[2]

To add on, Doherty et al. (2013) showed that crizotinib led to increased reactive oxygen species production, caspase activation, cholesterol accumulation, disruption in cardiac cell beat rate and blockage of ion channels. However, in "Comparison of Cardiovascular Effects of Crizotinib and Chemotherapy in Patients (pts) with ALK-Positive (+) Advanced Non-Small Cell Lung Cancer (NSCLC)," Wilner, Usari, Polli, and Kim (2016) found that the risk of cardiac failure does not increase when crizotinib is used, when compared to chemotherapy in patients with ALK-Positive NSCLC.[14] Additionally, in "Renal Effects of Crizotinib in Patients (pts) with ALK-Positive (+) Advanced Non-Small Cell Lung Cancer (NSCLC)," It was discovered that patients who were treated with crizotinib experienced in a decline in renal function over the first 2 weeks of treatment, however, there was no shown cumulative toxicity on prolonged treatment so the benefit/risk ratio for the usage of crizotinib remains positive.[6] In "ALK-Rearranged Non-Small Cell Lung Cancer is Associated with a High Rate of Venous Thromboembolism," Zer et. al (2016) argued that rate of venous thromboembolism (VTE) in patients who have the ALK-rearrangement is 3–5-fold higher than previously reported for the general NSCLC population.[15] This was supported in a study where 39% of patients who were treated with a TKI developed VTE when compared to the 18% of patients who were treated with chemotherapy who developed VTE.[15] Additionally, myelosuppression and infectious complications were the most common toxicity-induced adverse events that required.[9]

Because of the high percentage of patients who experienced these adverse events, and long length of the various adverse events, at first, crizotinib may not seem like a good choice of treatment of patients. However, patients who were treated with crizotinib had a significantly greater overall improvement from baseline in global quality of life, when compared to patients who were treated with pemetrexed, who had no significant improvement in global quality of life.[12] This claim was supported in a different study, where the patients claimed that they were not bothered by the most common adverse event of visual disturbances, allowing patients to continue treatment with crizotinib.[2] However, there is no evidence to prove that simultaneous usage of the aforementioned treatments would change the severity of the adverse events. It should be considered that some patients would not agree to subject themselves to simultaneously

using these two therapies, in fear of the unknown reaction of the adverse events. On the other hand, other patients may not mind this side effects, if it means that they are more responsive to these two therapies combined, allowing for a better progression free survival rate. There is also no evidence that suggests that simultaneously using crizotinib and pemetrexed will show a reduction from baseline in patients' global quality of life. Though the patients had increased amounts of side effects, the quality of life and progression free survival improved for patients treated with crizotinib. Thus, treatment should still be explored because it could be a life-saving treatment. Patients may not enjoy the adverse events, but they may just be a trade-off for a longer progression-free survival, and possibly longer overall survival rate.

5. Combating Resistance to Crizotinib

In order to combat the high percentage of patients that develop a resistance to crizotinib, second-generation TKI inhibitors could be used, such as Alectinib or Ceritinib, that usually do not result in a resistance. In "Overcoming Crizotinib Resistance in ALK-Rearranged NSCLC With the Second-Generation ALK-Inhibitor Ceritinib," Muller et al. (2016) claimed that most patients develop a resistance to crizotinib within 8 months (p. 147). In "ALK Alterations and Inhibition in Lung Cancer," published in the *Seminars in Cancer Biology*, Le and Gerber (2017) stated that Alectinib is active against both types of ALK that are associated with crizotinib resistance, and furthermore, patients who used Alectinib due to a crizotinib resistance had a 94% response rate in inhibiting lung cancer.[7] Additionally, patients who had CNS disease, and had developed a resistance to crizotinib, had a 52% response rate to Alectinib.[7] Even though Alectinib has shown promising numbers for patients who have developed resistance to crizotinib, there is still the problem of how patients should be treated, and what treatments they should receive and when, especially taking into consideration the order of treating patients with tyrosine kinase inhibitors.

Ceritinib is an ATP competitive tyrosine kinase inhibitor for ALK, and that in patients who were previously treated with crizotinib, there was an overall response rate of 56%, and the median progression free survival was 6.9 months (95% CI, 5.3 to 8.8).[7] The progression free survival appeared to be similar between patients with and without CNS disease at baseline. The impressive response of Ceritinib in both crizotinib-resistant and crizotinib-naïve patients may be attributed to several possible mechanisms: increased potency (20 times) against ALK, activity against ALK with secondary mutations in the tyrosine kinase domain, improved CNS activity, and/or inhibition of other tyrosine kinases not targeted by crizotinib, including IGF-1.[7] Progression-free survival seems to be improved when Ceritinib is used in the first line as compared to crizotinib, however, further head-to-head studies looking at different TKI sequencing will be needed to better clarify this question.[7] The complication with deciding which treatment to use involves the fact that the goal is to limit toxicity, while simultaneously increase the progression-free survival, and there is also the high cost of using two therapies at once.[7] To combat this, the search for and validation of new, more efficacious ALK-inhibitors are underway, such as brigatinib, entrectanib, loratinib, and belizatinib, for which outcomes data in ongoing clinical trials are pending.[7]

In addition to the development of newer generation ALK inhibitors other efforts have been made to overcome crizotinib resistance by targeting ALK function via ALK-independent pathways, such as inhibition of heat shock protein 90 (Hsp90), which is a molecular chaperone protein that guides the normal folding and turnover of intracellular growth factors and is used for the stabilization of several oncoproteins, such as ALK.[7] Inhibition of Hsp90 activity results in aggregation and degradation of its client proteins and disrupts associated signaling pathways involved in cellular proliferation, and that preclinical studies with Hsp90 inhibitors in EML4-ALK rearranged NSCLC cells demonstrated encouraging results.[7] This is further supported since it is stated that Hsp90 inhibitor 17-DMAG more potently inhibits the growth of the ALK-dependent human H3122 NSCLC cell line than crizotinib does, based off of previous in vitro work, which resulted in degradation of the ALK protein, rather than direct inhibition of kinase activity that crizotinib does.[1] Even though Hsp90 and immunotherapy are two other strategies used to overcome crizotinib resistance, they still are not potent for a second line defense as Ceritinib and Alectinib are. This is because Alectinib and Ceritinib are ALK Inhibitors, whereas Hsp90 targets ALK function via ALK-independent pathways, and immunotherapy focuses on the cell cycle at a molecular level.

6. Conclusion

Because patients with the ALK-Positive mutation who have ALK-Positive NSCLC are unresponsive to chemotherapy, show an increase in progression-free survival when treated with first-line crizotinib (targeted therapy) when compared

to pemetrexed chemotherapy, and develop a resistance to crizotinib over time, a study where treating crizotinib in combination with pemetrexed may be more successful in increasing progression-free survival, than both therapies separately. However, the big question is how ALK-positive NSCLC should be treated to maximize benefits, limit the toxicity and the cost, to ultimately increase the overall progression-free survival.

Crizotinib and pemetrexed simultaneously as a first line treatment could possibly be a better alternative to using either crizotinib or pemetrexed as a first line treatment, resulting in a higher progression-free survival of patients. However, complications and hindrances in this proposed study arise when the cost of the therapies, and the toxicity-induced adverse events are taken into consideration. Both aforementioned cost/benefit analyses of crizotinib claimed that it was not economically feasible, due to the high cost of drugs, and the low number of people in the population who have the specific biomarker of EML4-ALK fusion. Additionally, a high level of patients experienced grade 1-2 varying adverse events.

The possible resistance, high cost, and adverse events may seem like a deterrent to using crizotinib and pemetrexed, however, patients who were treated with crizotinib had a significantly greater overall improvement from baseline in global quality of life, when compared to patients who were treated with pemetrexed, who had no significant improvement in global quality of life.[12] This proposed treatment of combining crizotinib and pemetrexed should still be explored because it could result in a possible life-saving treatment. There may be a high cost of using both of the therapies at once, and there may be toxicity-induced adverse events that we have no knowledge of, and a resistance could develop, further studies should be done on combining crizotinib and pemetrexed, since it may result in a longer progression-free survival, and possibly a longer overall survival rate.

7. Acknowledgements

The author wishes to express their thanks and appreciation to Professor Mary Boyes and the faculty of the Honors College at Virginia Commonwealth University for their guidance and assistance.

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