Medicon Medical Sciences
Volume 1 Issue 4 November 2021
Mini-Review

Why do Molecular targeted Therapies in non-small Cell Lung Cancer have Limited Success?

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Received: October 13, 2021; **Published:** October 31, 2021

Abstract

In the last decade great strides have been made towards the discovery of molecules whose aberrant functioning has been held responsible for the genesis and progression of Non-Small Cell Lung Cancer (NSCLC). Broadly speaking there are two types of lung cancers: NSCLC, and Small Cell Lung Cancer (SCLC). The majority of lung cancers are of the type NSCLC. In this paper the therapeutic molecular targeting of aberrantly functioning molecule has been dealt with in the context of NSCLC, but, however, the conclusions derived in this paper hold for any molecular targeted therapy for any cancer. Different molecules are functioning aberrantly in different NSCLC patients, some of them being Mesenchymal–epithelial transition factor (MET), Kirsten Rat Sarcoma (KRAS), Epidermal Growth Factor Receptor (EGFR), etc. The paper analyzes the limited success of molecular targeted therapies in NSCLC in the context of MET inhibitors, and generalizes the results of analysis for any molecular targeted therapy against any cancer. The paper ends with the suggestion that the targeted molecular therapy in NSCLC be combined with the depressants of the Pentose Phosphate Pathway to improve patient response to the therapy.

Keywords: Clinical trial; Clinical success; Inhibitors; Proliferation; Apoptosis

Introduction

The success of the clinical trial of a therapy/drug against any disease is quantified in terms of Overall Response Rate (ORR), median Progression-free Survival (mPFS), median Overall Survival (mOS), median.

Duration of Response (mDOR), etc [24, 3, 18]. The clinical success in Non-Small Cell Lung Cancer (NSCLC) has been measured pre-dominantly by ORR, mPFS, mOS, and mDOR [17]. In this work we measure success by ORR and mPFS. ORR means the percentage of patients (who were given the therapy/drug) that showed reduction in disease to certain fixed degree. PFS means the duration (after the therapy/drug was given to patient) for which the disease was stable without worsening.

Based on the different molecules which demonstrate abnormalities either at the molecular level or genetic level in a particular NSCLC patient, the NSCLC can be categorized into following sub-types [17]

(i) Mesenchymal–epithelial transition factor (MET) NSCLC
(ii) Rearranged during Transfection (RET) NSCLC
(iii) Neurotrophic Tyrosine Kinase (NTRK) NSCLC
(iv) Kirsten Rat Sarcoma (KRAS) NSCLC
(v) Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic subunit Alpha (PIK3CA) NSCLC
(vi) Human Epidermal Growth Factor Receptor 2 (HER2) NSCLC
(vii) Epidermal Growth Factor Receptor (EGFR) NSCLC

(viii) Anaplastic Lymphoma Kinase (ALK) NSCLC

(ix) c-Ros Oncogene 1 (ROS1) NSCLC

(x) v-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) NSCLC

At least the 10 sub-types of NSCLC have been listed above, indicating that the deregulation of any one of at least the 10 different types of most upstream oncogenic molecule respectively lead to a particular sub-type of NSCLC. In this paper I analyze the level of success of inhibitors against MET from the clinical trial results in patients suffering from (MET) NSCLC. I do not stop here but I also hypothesize first (in this paper) the causes behind the observed level of success of inhibitors in the context of (MET) NSCLC patients. Thereafter I generalize the results of my study for the patients suffering from all the other sub-types of NSCLC and not (MET) NSCLC alone. The most common abnormalities observed in the MET molecule/gene in (MET) NSCLC patients are over-expression, amplification, and exon14 skipping mutations (METex14) [17]. Some of the molecular abnormalities (of a particular molecule) may also appear in combination with other deregulated molecules, for eg, MET amplification may occur in an (EGFR) NSCLC patient. Table 1 lists the maximum values of ORR and mPFS observed in clinical trials of inhibitors against MET in advanced (MET) NSCLC patient.

Only Capmatinib in METex14 patients, and Tepotinib + EGFR Inhibitor in MET amplification+(EGFR) NSCLC patients have noticeable success. Otherwise the MET inhibitors have very limited success. But, however, even in the case of the clinical trial of Capmatinib in METex14 patients, 32% patients showed no response (to required degree). Ideally ORR should be so close to 100% as possible. In next section I analyze the causes behind the limited success of MET inhibitors (against (MET) NSCLC patients), in general.

DRUG	***ABNORMALITY***	***Maximum ORR (amongst all trials)***	***Maximum mPFS (amongst all trials)*** ***(In months)***
Crizotinib	METex14	40%	7.3
Capmatinib	METex14	68%	12.4
Tepotinib	METex14	50%	11.0
Savolitinib	METex14	47.5%	6.8
Capmatinib	MET amplification + (EGFR) NSCLC	29%	4.1
Tepotinib + EGFR Inhibitor	MET amplification + (EGFR) NSCLC	67%	16.6
Capmatinib + EGFR Inhibitor	MET amplification + (EGFR) NSCLC	47%	--------
Cabozantinib + EGFR Inhibitor	MET amplification + (EGFR) NSCLC	10.8%	3.6

Table 1: Overall Response Rate and median Progression-free Survival observed in clinical trials of inhibitors against Mesenchymal-epithelial transition factor in advanced Mesenchymal–epithelial transition factor Non-Small Cell Lung Cancer patients (source: Reference 17).

The Limited Success of MET inhibitors (against (MET) NSCLC patients)

The partial cause for the limited success of MET inhibitors could be a non-hundred percent efficiency of binding of these MET inhibitors to MET extracellular domain. But, however, this is not the end of the story. There are two other ends of the story, the first amongst them being discussed below.

The activation of MET deregulates proliferation and apoptosis through the activation of following four downstream signaling pathways [17]

(a) MAPK (mitogen-activated protein kinase)-ERK (extracellular signal-regulated kinase) pathway
(b) PI3K (phosphatidylinositol 3-kinase)-AKT (protein kinase B) pathway
(c) mTOR (mammalian target of rapamycin) pathway
(d) JAK (Janus Kinase)-STAT (signal transducer and activator of transcription) pathway

In the MAPK-ERK pathway downstream of deregulated MET is Ras molecule, downstream of Ras is Raf molecule; and in many cancers Ras or Raf has been found to be mutated [6]. In many instances even the nuclear transcription factors of MAPK-ERK signaling pathway, myc and AP-1 have been found to be mutated [6]. Through its nuclear transcription factors MAPK-ERK pathway has been known to control proliferation, differentiation, apoptosis, and migration. The MET inhibitor will fail if any one amongst the three, Ras, Raf, or myc, or any combination of these three is mutated. The role of AP-1 in causing the apoptosis of cell is unsettled [2]. Notably, the cancer patients with deregulations in the genes of the MAPK-ERK pathway have shown poor prognosis [21].

PI3K is a big family of molecules; only class IA PI3K is known to have role in malignant transformation of cells. Unless otherwise specified, PI3K will mean class IA PI3K. PI3K has two subunits: the p85 subunit is regulatory which attaches through its SH2 domain to the receptor tyrosine kinases like MET, and the p110 subunit is catalytic which is attached to the p85 subunit through inter-SH2 domain (of p85) [25]. p110 catalyses the conversion of phosphatidylinositols PtdIns (4, 5) P_2 (PIP_2) to PtdIns (3,4,5) P_3 (PIP_3). Under normal conditions when PI3K is not in contact with receptor tyrosine kinases, p85 has inhibitory effect on p110. PIP_3 plays the important role of activating AKT signaling pathways downstream of MET-PI3K, and this deregulates cell growth, proliferation, and apoptosis. One of the signaling pathway activated by activation of AKT is mTOR, which we will discuss later separately. One of the important apoptotic molecule in interaction with PI3K-AKT pathway is PTEN [25]. Popularly known as tumor suppressor protein, PTEN converts PIP_3 back to PIP_2, thereby preventing the accumulation of PIP_3 in cell and leaving AKT in inactivated state. Hence PTEN causes apoptosis because activated AKT has been known to block many genes causing apoptosis. The gain-of-function mutation has been observed in p110 alpha protein (PIK3CA) in lung cancer (along with cancers of several other organs) [16]. The MET inhibitor will fail if p110 alpha protein is mutated. However, given the modus-operandi of PTEN, MET inhibitor will not fail if PTEN has undergone loss-of-function mutation. It is a possibility that as further research is done in profiling mutations in NSCLC, the genes of the AKT pathway may too be found to be mutated. If it is so, then MET inhibitor will fail for these mutations too.

mTOR is the general name of two classes of molecules, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), both of which are different from each other in their sensitivity towards rapamycin [23]. Together both control cell proliferation, cell survival, cell migration, cell metabolism and autophagy; and it has been hypothesized in [23] that several sub-units/components of the mTOR complex/pathway are mutated in a large number of cancers. The mTOR complex which responds to MET activation is mTORC1, and through regulatory controls by MAPK-ERK and PI3K-AKT pathways, both of which are upstream to the mTORC1 pathway. Hence, MET inhibitor will fail if genes of the mTORC1 complex/pathway are mutated. It will be interesting to test the combined therapy of MET inhibitor with mTOR inhibitor.

The STAT family comprises 7 transcription factors STAT 1-4, STAT 5A, STAT 5B, and STAT 6. Out of these STAT3 has been found to be active in NSCLC [22, 14, 11]. The STAT is active when JAK becomes active upon the binding of the ligand to receptor c-MET (in the context of (MET) NSCLC). Alternatively STAT3 becomes active upon up-regulation of the mTOR signaling [23]. In NSCLC and a majority of solid tumors, unlike hematological malignancies, mutations in STAT3 gene have not been found and that the activation of STAT3 has been found to be because of the activation of JAK through several mechanisms involving a multitude of ligand-receptor combinations [22, 14, 11]. The active STAT3 has direct role in the transcription of a multitude of genes controlling cell proliferation, differentiation, and apoptosis. Out of the four signaling pathways de-regulated by MET activation, this is the one which is odd one out, i.e., for MET acting through JAK-STAT pathway the MET inhibitor will not fail.

The analyses presented above is generalized in Table 2 below for the success/failure of any molecular targeted therapy against any cancer.

Case No	*Case of Malignant Transformation*	*Result*
1.	The most upstream oncogenic molecule activated + No direct deregulation of the genes in signaling pathways downstream of the molecule	The inhibitor against the activated most upstream oncogenic molecule will succeed.
2.	The most upstream oncogenic molecule activated + Direct deregulation of the genes in signaling pathways downstream of the molecule such that apoptosis is prevented but proliferation is not enhanced	Through clonal evolution [9], direct deregulation of signaling pathways downstream of the molecule will enhance proliferation too. The inhibitor against the activated most upstream oncogenic molecule will fail.
3.	The most upstream oncogenic molecule activated + Direct deregulation of the genes in signaling pathways downstream of the molecule such that proliferation is enhanced but apoptosis is not prevented	Through clonal evolution [9], direct deregulation of signaling pathways downstream of the molecule will down-regulate apoptosis too. The inhibitor against the activated most upstream oncogenic molecule will fail.
4.	The most upstream oncogenic molecule activated + Direct deregulation of the genes in signaling pathways downstream of the molecule such that proliferation is enhanced, and apoptosis is also prevented	The inhibitor against the activated most upstream oncogenic molecule will fail.

Table 2: Success/failure of any molecular targeted therapy against any cancer.

The third end of the story of limited success of any molecular targeted therapy against any cancer is that through clonal evolution [9], the targeted molecule undergoes subtle structural changes so that the inhibitor fails to bind the molecule.

The Therapeutic Solution

The therapeutic solution to the problem of limited success of molecular targeted therapy against any cancer must lie in a cancer biology more fundamental (fundamental in the sense that the said cancer biology is common to most of the cancers) than the multitude of signaling pathways and their networks particular to the targeted molecule. For many years the scientists have believed that cancer cells have enhanced aerobic glycolysis, popularly known as the Warburg effect [5]. But the research in recent years show that the glucose metabolic pathway having a more dominant effect on carcinogenesis than glycolysis is pentose phosphate pathway (PPP) [1]. In work [20], a hypothesis named Fooling of Homeostasis Hypothesis (FHH) [19], states that in cancers which have stem cell basis PPP is up-regulated. Notably, NSCLC is known to have stem cell basis [15]. Enhanced PPP has been linked with many cancers, including the cancers of the lung, in recent years [8, 13, 10]. PPP has a very tight control on proliferation and apoptosis through interactions with a multitude of signaling pathways and their networks. Enhanced PPP causes enhanced proliferation and reduced apoptosis, whereas down-regulated PPP leads to reduced proliferation and enhanced apoptosis [1]. So, I propose that the targeted molecular inhibitor be combined with depressants of the PPP, to increase the success of targeted molecular inhibitors. The well known depressants of the PPP are ethanol-alcohol dehydrogenase and sodium metabisulphite [4]. These chemicals can be loaded on a particular monoclonal antibody targeted against the particular bio-marker exclusive only to the particular cancer being treated [12].

Conclusions

Though the study above was conducted for advanced (MET) NSCLC patients, the results hold for all the other sub-types of NSCLCs, and even also for early stage NSCLCs. The molecular targeted therapies in early stage NSCLCs too have been shown to have limited success [7]. The major cause of the said limited success seems to the direct de-regulation of the apoptotic and or proliferation genes or pathways regulating those genes in addition to the oncogenic activation of the most upstream oncogenic molecule. As the days of clinical trials of the molecular targeted therapies in NSCLC patients pass, despite the initial success the patients start exhibiting resistance to the inhibitors and the most probable primary cause being the slight changes in the structures of extra-cellular domains of the molecules which are being targeted. So efficacy enhancement in molecular targeted therapies seem a challenge, but the author suggests that the challenge can be met by combining molecular targeted therapies with depressants of the Pentose Phosphate Pathway.

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