

Role of NRG1 Coalescence for Treatment of Lung Cancer in Patients

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ABSTRACT

Gene-targeted treatments for lung cancer have significantly increased survival rates when compared to conventional chemotherapy. In both Europe and the United States, researchers are looking into the therapeutic potential of a gene fusion called Neuregulin 1 (NRG1). The purpose of this review is to highlight the importance of this novel fusion in the treatment of lung cancer and the most recent achievements in this field. In a broad spectrum of cancers, oncogenic gene fusions originate from structural DNA rearrangements that promote uncontrolled cell proliferation. The genes of cross-breeds As a result, drugs to inhibit cell growth and proliferation have been created. Lung cancer therapy is increasingly focusing on oncogene fusions such as ALK, RET, NTRK, and ROS1, among others. Many diseases have been linked to NRG gene fusions, which have been linked to a variety of solid tumours (including kidney and pancreatic cancer, breast and colorectal cancer, and lung cancer). As has been the case for decades, oncology treatment will continue to evolve, moving from a focus on the disease's genesis to a more genetically-based approach. In addition to improving survival rates, the increased availability of these drugs has sparked a renewed interest in finding new therapies.

Keywords: Multiplex technique; NRG gene; Molecular indicators; Oncogenic gene fusions

INTRODUCTION

Medical oncology's diagnostic and treatment options are becoming more personalized, and that trend will only accelerate. A patient's prognosis, responsiveness to therapy, and survival will be aided by the presence or absence of particular genetic anomalies. A slew of pharmaceuticals have been given FDA targeted therapy approval in the previous ten years. There are a number of gene abnormalities that may be targeted, including EGFR, BRAF, ROS, RET; KRASg12c; NTRK; PD1; IDH1/2 and FGFR. As a result of this, questions have been raised concerning the usefulness of other molecular indicators, as well as blood tests, such as liquid biopsies. When DNA reorganization results in uncontrolled activity, oncogenic gene fusions occur.

The 8p12 region of chromosome 8 may contain the NRG1 gene. One of the growth factors produced by this gene is Neuregulin 1 (NRG1). When the Ebb/HER receptor complex interact with NRG1's tyrosine kinase ErbB3, it activates downstream signaling pathways that result in cell proliferation. There may be EGF-like

domains in NRG1. As a result, drugs that specifically target NRG1 are now being researched.

LITERATURE REVIEW

Expression of NRG1

KRAS and ALK are known proto-oncogenes that may generate NRG1 rearrangements. Cancer patients with various mutations may now be treated with TKI drugs, which target a wide range of different receptors and genetic abnormalities in the same tumor. A wide variety of malignancies, not only those with single-mutation receptors, may benefit from the use of TKIs.

The expression of NRG1 has been shown to be adaptable in non-neoplastic conditions. In-depth discussions have been held on the cardiovascular, gastrointestinal, and neurological systems. When cardiomyocytes are injured or overworked, the expression of NRG1 increases, resulting in the activation of fibroblasts and macrophages, which may contribute to the development of heart failure. To provide an example, researchers have shown that

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NRG1 may help to enhance cardiac function in a number of heart failure models, and the compound is currently being investigated in atrial fibrillation in addition to other cardiac disorders, such as Hirschsprung's disease [1].

Even if the NRG1 gene is not present in the nervous system, Alzheimer's disease may still arise. CSF NRG1 expression has been discovered to have a negative association with cognition in Alzheimer's disease patients; according to Mouton-Liger et al. Cortical stroke treatment has been demonstrated to have a protective effect on persons with schizophrenia who have a positive association between cognition and schizophrenia [3].

NRG1 reports in lung Cancer

More than a dozen malignancies have been linked to alterations in NRG1. Tumors were found in 0.2 percent of the 21,858 tissue samples studied by Janna and her colleagues. Non-Small Cell Lung Cancer (NSCLC) was the most seen kind of lung cancer (NSCLC). Besides prostate and colorectal cancer, there have been reports of NRG1 fusions in various forms of cancer, including digestive tumors, squamous cell carcinoma, and breast cancer, other tumor types that have been linked to NRG1 fusions include prostate and colorectal cancers, as well as squamous cell carcinoma As well as squamous cell carcinoma (sarcoma). Clinically, these tumors can be treated. NSCLC cancer cases, specifically adenocarcinomas, were found to have NRG1 rearrangements in 0.14 percent (3/2079) of the cases, while pancreatic adenocarcinomas had NRG1 rearrangements in 0.13 percent (1/791) of the cases, and breast cancer cases had NRG1 rearrangements in 0.04 percent (1/2703) of the cases. NRG1 fusions were found in 11% of patients having wild-type KRAS of lung cancer, which is a significant finding (4 of 36). (4/18/36) Researchers Fernandez-Cuesta et al. suggested that among nonsmokers, Smokers are more likely to have NRG1 alterations than nonsmokers. NRG1 was found in four of the 15 IMA subtypes of lung adenocarcinoma after screening 102 tumors with no known oncogenic alterations (IMA).

Patients with lung IMA NRG1+ received alemtuzumab, an anti-ERBB3 antibody, in an exploratory treatment study published in Cancer Research. Both patients were treated with the assumption that they had failed at least three previous rounds of treatment and needed a new approach. Without experiencing any unacceptable toxicity, a PFS of at least sixteen weeks was possible. Since NRG1 rearrangements are common in IMA patients, more research into novel treatment approaches, such as targeting HER2, is warranted, given the rarity and severity of this disease (Figure 1). According to many investigations, such as that conducted by Hogarth et al., modifications to NRG1 result in both cell proliferation and apoptosis escape when certain mutations occur, whereas other mutations and protein fusions result in cell death. Scientists believe that both the overexpression and the down regulation of this mechanism might increase cellular proliferation in the body. In light of this hypothesis, more study is needed to establish whether tumor regression may be caused by both inhibiting this mechanism and eliminating agonist. It is possible that identifying activating fusions of NRG1 may need some care, regardless of whether or not this is the answer.

Diagnosis and treatment of lung cancer

For women with ERBB2-positive breast cancer, the cornerstone of treatment is a single session of targeted therapy. Trastuzumab resistance may be caused in Yang et AL studies by an increase in the expression of NRG1 in the cancer cells. Because this gene aberration may show not only another type of targetable receptor, but also a modifiable receptor that may be utilized to prevent resistance to anti-HER2 therapy, researchers are more interested than ever in this gene aberration. Rearrangements of NRG1 in breast cancer have been shown to be a poor prognostic factor [1-6].

When chemotherapy is used alone or in combination with surgery or radiation therapy, it is the more common type of lung cancer treatment. Relapsed or resistant patients may benefit from the use of Next-Generation Sequencing (NGS) in order to find the best therapeutic choice for them. Increasing NRG1 expression in tumor cells may counteract the toxic effects of chemotherapy, which might lead to treatment resistance, say Hedge et al. This study analyzed six patients with NRG1 gene fusions, five of whom were diagnosed with LMA and one with CRC, according to the authors, who all received afatinib for their treatment. Only one of the five patients who received therapy for lung cancer achieved a Complete Remission (CR), while four of the five had Partial Responses (PR) (SD). The CRC patient had an excellent prognosis [5-10]. In order to participate in the research, most patients had previously tried and failed a number of other treatments before being accepted. This case continuity suggests that NRG1 inhibitors may be a chance for those who have tried a variety of treatments. According to the study's authors, afatinib was used to treat three of 47 individuals with NGR1 rearrangement. Then there is Jones, too. Genome sequencing in all three cases showed a wild-type KRAS gene. NRG1 was discovered in gene fusions with wild-type KRAS in KRAS malignancies. Because their tumors were NRG1 fusion positive, both patients responded to Afatinib. These patients included one who had previously battled colon and stomach cancers, as well as one who had previously dealt with cancers of the prostate and the urethra. As more studies come to light showing that the NRG1 mutation increases one's risk of developing a wide range of malignancies, it may be used as genetic marker in future liquid biopsy procedures. Overexpression of NRG1 and activation of a parallel pathway in HER2-positive for breast cancer models as well as ALK-positive lung cancer models may explain resistance to NRG1-targeting medicines, according to their results. According to the study by Yung et al., 28.1 percent of the 502 gastric cancer samples analyzed (141 individuals) were positive for NRG1. High pathological stage and poor prognosis have been linked to NRG1 overexpression although these traits have not been proved to be associated with NRG1's presence. Examples of aggressive cancer features include infiltrative tumor growth, lymph venous invasion, and brain invasion. Researchers in this study discovered that high levels of NRG1 expression were linked to poor clinical outcomes, which implies that drugs that specifically target NRG1 might be useful in the treatment of gastric cancer. According to Duruisseaux et al., reported of 25 French patients having IMA was published in a medical publication. One ROS1 rearrangement, 12 KRAS mutations,

and one ALK rearrangement were the most prevalent mutations detected in 14 of the 25 IMAs (4 percent). Eleven of the pan-negative IMAs analyzed had NRG1 rearrangements. Rearrangement of the NRG1 gene was carried out on a Vietnamese woman, who was aged 61 and had never smoked. Prior to her current diagnosis, this woman had had neoadjuvant chemotherapy and radiation treatment for breast cancer.

There are two main conclusions the authors have drawn. NRG1 FISH testing should be performed in people having pan-negative IMA, as well as patients of Asian descent are more likely to have NRG1 abnormalities than non-Asian patients with IMA. In order to draw conclusions from these findings, the study's small sample size must be considered. In the *Annals of Oncology*, a two-case study by Jones et al. was published. Patients with cholangiocarcinoma and lung cancer had their NRG1 rearrangements quite different from one another; however the TKI afatinib was employed to treat both of them throughout their chemotherapies. Responses in both patients were statistically significant and sustained (Figure 1) [11-17].

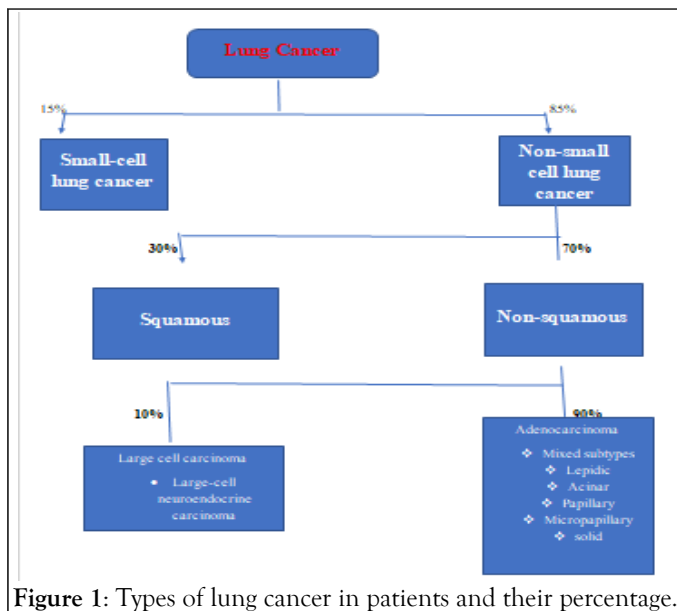


Figure 1: Types of lung cancer in patients and their percentage.

NRG Studies about treatment

The eNRGy1 Global Multicenter Registry just released new data. In the greatest retrospective study to date, the clinical and pathological qualities of lung cancer carrying patients with NRG1 rearrangements were studied, giving important information on diagnostic processes and therapy response rates for conventional therapies... There were more NRG1 gene fusions found in non-metastatic people (71%) and those who had never smoked (57%) than in those who did (57 percent). At the very least, 57% of the population. Quantity (57 percent) RNA sequencing has a higher detection rate than DNA sequencing. Among patients with NRG1 rearrangements, the median PFS was 5.8 months for those patients who received chemotherapy (ORRs of 13% as well as 14%, respectively; while median PFS of 4.0 months in those patients who received chemotherapy) as well as 3.6 months for those patients who acquire immunotherapy alone (ORR of 20%; median PFS of 3.6

months) (ORR 20 percent as well as PFS 3.6 months). Those Patients with metastatic disease who received afatinib showed good outcomes (ORR of 25% and PFS of 2.8 months) without regarding fusion partner. Reports by Laski et al. demonstrate a range of three to 36 months of response in a 19-case study of patients having various kinds of cancer. It's possible that the NRG1 gene is a useful prognostic factor, although current results are unclear, according to this research. More than half of the 115 surgical specimens evaluated by Pan and colleagues included NRG1 mutations, which may explain the association between NRG1 expression and Overall Survival (OS) and lower risk of recurrence after lung cancer resection. Patients with IMA who had NRG1 rearrangements may have additional driver mutations, such as KRAS and ALK fusions (10/16 NRG1 fusion-positive cases, and two additional instances, respectively, Shin et al. reported). An SLC3A2-NRG1 having rearrangement was combined with a worse overall survival rate in the study (OS).

A novel molecular subgroup has been identified by NRG1 mutations, paving the way for more research studies. The NRG1 gene was initially studied for its activity in cardiac, neurological, and gastrointestinal tissue development and response to injury and disease. Is considered as an oncogene of enhancing significance, with therapeutic implications for personalized medicine. Future research will include more people and a broader range of tumors, including those that aren't lung cancer, as we gain more insight into this mutation's prevalence and impact [18-22].

CONCLUSION

The mechanisms of resistance for this combination regimen will need more investigation. The development of medications for rare illnesses is difficult, but evaluating pharmaceuticals that have already been approved for other uses is an option worth considering. Individualized treatment choices for lung cancer include expanded with the use of multiplex techniques that can identify a variety of drug gable gene fusions. Considering the prevalence of NRG1 fusions in cancer patients, it is crucial to look for novel drugs that may have significant therapeutic benefits.

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